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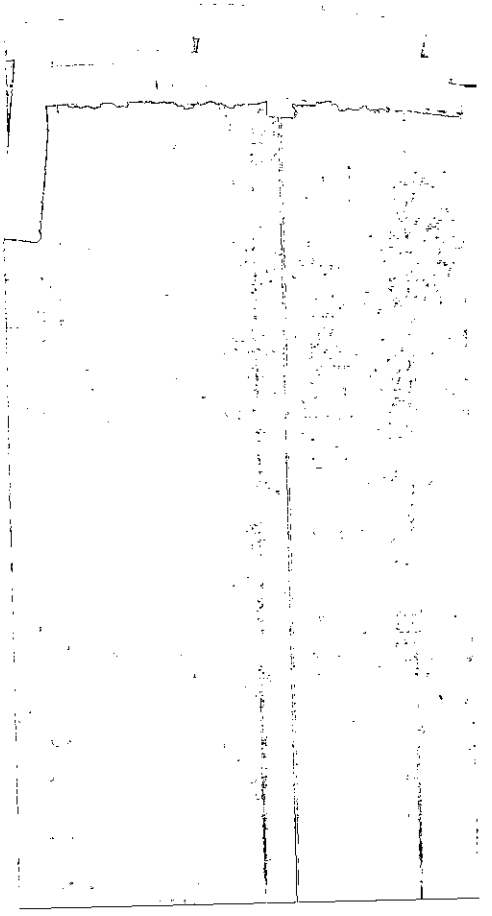

PART ONE

THE HYDRATION EQUILIBRIUM OF ISOBUTYRALDEHYDE

PART TWO

CATALYST STUDIES IN DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-D

A THESIS

Presented to

the Faculty of the Graduate Division

by

James Grey Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

in the School of Chemistry

Georgia Institute of Technology

September, 1964

PART ONE

THE HYDRATION EQUILIBRIUM OF ISOBUTYRALDEHYDE

PART TWO

CATALYST STUDIES IN DEUTERIUM EXCHANGE OF ISOBUTYRALDEHYDE-2-D

Approved:

Date approved by Chairman: May 10, 1965

ACKNOWLEDGMENTS

I wish to thank Dr. Jack Hine for his many hours of patient supervision during this work. Without his guidance I would have quit long ago. I am grateful to Dr. J. R. Cox, Jr. and Dr. John R. Dyer for serving on the reading committee. I also wish to thank my fellow students in both the graduate school and the undergraduate school who have helped in their various ways.

I am also grateful to Dr. William M. Spicer for having selected me as a recipient of a National Defense Education Act Fellowship.

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SUMMARY

PART ONE

The kinetics of the acid-catalyzed hydration of isobutyraldehyde was studied using nuclear magnetic resonance spectrometry. The equations used for determining the first-order rate constant of rapid reactions from changes in line shapes in the nuclear magnetic resonance spectra, as developed by McConnell and used by Charman, Vinard, and Kreevoy, were applied to the hydration reaction. The second-order rate constant for acid-catalyzed hydration was found to be 442 ± 24 $l.-m.^{-1}-sec.^{-1}$ at 35°. This value is in reasonable agreement with the studies of the hydration of isobutyraldehyde and acetaldehyde by Bell, McTigue and coworkers who used calorimetric kinetic techniques.

Values of 0.604 at 25° and 0.423 at 35° were obtained for the hydration equilibrium constant using nuclear magnetic resonance techniques.

PART TWO

As the initial step in the study of polyfunctional catalysis of removal of protons alpha to carbonyl groups, a kinetic study was made of the deuterium exchange of isobutyraldehyde-2-d catalyzed by a variety of tertiary amines and oxygen bases. The kinetics were followed by the analysis of the nuclear magnetic resonance spectrum of the isobutyraldehyde in the reaction mixture.

A Bronsted catalysis equation correlation of the basicity of three unhindered pyridines and seven phenoxide ions with their second-order rate constants for deuterium exchange is satisfactory with β's of approximately 0.5. However, pyridines with 2- and 6-substituents are less reactive than predicted by the Bronsted equation, by more than 100-fold in the case of 2,6-lutidine and 2,4,6-collidine. This is the largest rate-depression reported for reactions with proton removal as the rate determining step. This result indicates that the proton-removal step is sterically hindered.

Further indication of steric hindrance can be seen in the rate constants for exchange catalyzed by saturated amines. If the value of β is determined from a Bronsted plot of the two most reactive unhindered amines--triethylenediamine and trimethylamine--it is found that triethylamine and triethanolamine, for which the greatest hindrance would be expected, are less reactive than anticipated by 40-fold and 1000-fold, respectively. The other tertiary amines studied are less active than triethylenediamine and trimethylamine, considerably more reactive than

the hindered amines and seem to fit the Bronsted catalysis equation for the phenoxides or unhindered pyridines roughly. The reactivity of N-methylimidazole as a catalyst is less than would be expected from an unhindered pyridine with similar basicity. The fact is attributed to the fact that the molecular geometry of an imidazole changes much more on protonation than does that of a pyridine.

The study of trimethylamine-N-oxide catalysis of deuterium exchange of isobutyraldehyde-2-d indicates that the amine oxide reactivity is small enough that the oxidation of small amounts of the tertiary amines used in this study to amine oxides will not significantly complicate determinations of catalytic constants for the tertiary amines. Trimethylamine-N-oxide is a better catalyst than acetate ion, but only slightly better than an unhindered pyridine of its basicity would be. From a Bronsted plot of the phenoxide ions, trimethylamine-N-oxide appears to have the reactivity expected of a phenoxide ion of its basicity.

The base-catalyzed dealdolization of isobutyraldol was studied to learn the relative rates at which the carbanion added to aldehyde and was protonated under various conditions. Except with catalysts that are relatively strongly basic but relatively unreactive, the intermediate carbanions formed should be protonated so much faster than they add to other aldehyde molecules that aldolization should not be able to compete with deuterium exchange.

Deuterium exchange catalyzed by a two-component catalyst was examined to learn whether catalysis via enamine formation would be observed. A catalyst composed of a N-methylmorpholine-N-methylmorpholinium perchlorate buffer and methylammonium chloride was studied. The

small amount of methylamine present forms an immonium ion intermediate from which the N-methylmorpholine removes the deuteron. The kinetics of the exchange indicate a term first order in N-methylmorpholine and first order in methylammonium ion. Also, of course, there is a term first order in N-methylmorpholine for the direct removal of deuterium from the aldehyde.

PART ONE

CHAPTER I

INTRODUCTION

In the course of kinetic studies of isobutyraldehyde using nuclear magnetic resonance spectrometry, the possibility of studying the rate of acid-catalyzed hydration presented itself. Subsequently Gruen and McTigue (1) reported the study of the rate of hydration using calorimetric techniques at 25°; they report the catalytic constant for the hydrogen ion case to be 1200 $l.-m.^{-1}-sec.^{-1}$. It would be of interest to compare the results obtained by calorimetry with nuclear magnetic resonance techniques.

From the work of McConnell (2) concerning the study of reaction rates by nuclear magnetic resonance, a series of equations were obtained, which when treated properly would permit the study of the rate of a fast reaction such as the hydration of isobutyraldehyde. These equations are modifications of the equations presented by Bloch (3) in his explanation of the phenomena of nuclear magnetic resonance. The equations have been used by several workers in studies of chemical exchange reactions (4, 5,

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1. L. C. Gruen and P. T. McTigue, J. Chem. Soc., 1963, 5224.

2. H. M. McConnell, J. Chem. Phys., 28, 430 (1958).

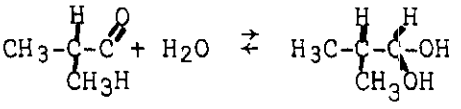
3. F. Bloch, Phys. Rev., 70, 460 (1946).

4. H. S. Gutowsky, D. W. McCall and C. P. Slichter, J. Chem. Phys., 21, 279 (1953).

5. H. M. McConnell and S. B. Berger, J. Chem. Phys., 27, 230 (1957).

6, 7, 8).

These equations can be used to study a simple chemical exchange system where a rapid, reversible molecular process transfers a hydrogen nucleus, H, between two molecular environments. This process is, in the case to be studied, the rapid hydration-dehydration of isobutyraldehyde.



The following notation is that of Bloch and McConnell:

1. $1/\tau_B$ is the first-order rate constant, k_B, for the change of compound B to compound A. $1/\tau_A$ is the first-order rate constant, k_A, for the change of compound A to compound B.

2. U is the component of H nuclear magnetism that is in phase with the effective rotating component of the rf field.

3. V is the component of H nuclear magnetism that is out of phase with the rotating rf field.

4. M_Z denotes the component of H nuclear magnetism in the direction of the large rotating field.

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6. E. Grunwald, A. Loewenstein and S. Meiboom, J. Chem. Phys., 27, 630 (1957).

7. H. S. Gutowsky and A. Saika, J. Chem. Phys., 21, 1688 (1953).

8. H. B. Charman, D. R. Vinard and M. M. Kreevoy, J. Am. Chem. Soc., 84, 347 (1962).

5. ω_A and ω_B are the frequencies at which the signals being described are at a maximum intensity for compounds A and B, respectively.

6. ω_1 is the frequency at which the signal is being described.

These magnetizations can be considered to be the sum of the contributions of the molecules in the form A and the molecules in form B (in this case isobutyraldehyde is defined as form B and its hydrate form A).

$$\underline{U} = U_A + U_B$$
$$\underline{V} = V_A + V_B$$
$$M_Z = M_Z^A + M_Z^B$$

$\Delta\omega_A$ and $\Delta\omega_B$ are the differences in cycles per seconds between the frequency at which the signal is being observed, ω_1, and the frequency of the signal maximum for compound A and compound B, respectively.

The modified Bloch equation as presented by McConnell are:

$$\dot{U}_A + \Delta\omega_A V_A = \frac{-U_B}{\tau_{2A}} + \frac{U_A}{\tau_B}$$

$$\dot{U}_A + \Delta\omega_B V_B = \frac{-U_B}{\tau_{2B}} + \frac{U_B}{\tau_B}$$

$$\dot{V}_A - \Delta\omega_A U_A = \frac{-V_A}{\tau_{2A}} + \frac{V_B}{\tau_B} - \omega_1 M_Z^A$$

$$\dot{V}_B - \Delta\omega_B U_B = \frac{V_B}{\tau_{2B}} + \frac{V_A}{\tau_A} - \omega_1 M_Z^B$$

The terms τ_{2A} and τ_{2B} are defined by the following relationship between the transverse relaxation times (T_{2A}) of the nucleus H in system A and the first-order lifetime of H in A.

$$1/\tau_{2A} = 1/T_{2A} + 1/\tau_A$$

The same relationships apply for system B. For ease of handling the equations the following notation will be used:

$$C_A = 1/\tau_{2A} \qquad \delta_A = \Delta\omega_A$$

$$k_A = 1/\tau_A \qquad M^A = M_Z^A$$

The same notation will also apply to system B. The equilibrium constant for the hydration of isobutyraldehyde, K, is equal to $[IBAOH_2]/[IBA]$ where $[IBAOH_2]$ is the concentration of isobutyraldehyde hydrate and [IBA] is the concentration of isobutyraldehyde. Charman, Vinard, and Kreevoy (8) use C for the equilibrium constant.

Making the notation changes and assuming slow passage the equations 1-4 become:

$$\delta_A V_A = - U_A C_A + U_B k_B \qquad (1)$$

$$\delta_B V_B = - U_B C_B + U_A k_A \qquad (2)$$

$$-\delta_A U_A = -V_A C_A + V_B k_B - \omega_1 M^A \qquad (3)$$

$$-\delta_B U_B = -V_B C_B + V_A k_A - \omega_1 M^B \qquad (4)$$

By algebraic manipulations equations 1-4 will give the signal height at a given frequency, that is to say $V_A + V_B$ or $\underline{V}$ the total signal at the frequency of the B signal maximum.

By solving for $V_A + V_B$ and substituting in the original notation, the following solution can be obtained.

$$\frac{-\underline{V}}{\omega_1} = -\frac{[(1/\tau_{2A} + 1/\tau_B)M_Z^B + (1/\tau_{2A} + 1/\tau_A)M_Z^A]\,[1/\tau_A\tau_B - \tau_{2A}\tau_{2B} + \Delta\omega_A\Delta\omega_B]}{[1/\tau_A\tau_B - 1/\tau_{2A}\tau_{2B} + \Delta\omega_A\Delta\omega_B]^2 + [\Delta\omega_B/\tau_{2A} + \Delta\omega_A/\tau_{2B}]^2} + \frac{(M_Z^B\Delta\omega_A + M_Z^A\Delta\omega_B)\,(\Delta\omega_A/\tau_{2B} + \Delta\omega_B/\tau_{2A})}{[1/\tau_A\tau_B - 1/\tau_{2A}\tau_{2B} + \Delta\omega_A\Delta\omega_B]^2 + [\Delta\omega_B/\tau_{2A} + \Delta\omega_A/\tau_{2B}]^2} \qquad (5)$$

The equation disagrees with equation 2 of Charman, Vinard and Kreevoy in sign; also the final term in the numerator of their equation appears to have a typographic error, 2A should be τ_{2A} and 2B should be τ_{2B}.

Equation 5 becomes Equation 3 of Charman, Vinard and Kreevoy if the frequency, ω_1, at which the signal is observed is the signal maximum of form B of the aldehyde. This means that δ_B is zero. Since the only δ left is δ_A it is referred to as δ. The rate constant for the forward reaction, $1/\tau_B$, divided by the rate constant for the reverse reaction, $1/\tau_A$, is equal to K. M_Z^A/M_Z^B should also be equal to K since these terms are proportional to the concentrations of A and B. By making these sub-

stitutions and substituting ξ_A^o for $1/T_{2A}$ and ξ_B^c for $1/T_{2B}$ an equation is obtained that is made up of experimentally obtainable parameters.

$$\frac{V_B}{M_Z^B\omega_1} = \frac{\{[\xi_A^o + k_B(1 + 1/K)] + [\xi_B^o + k_B(1 + 1/K)]K\}\{Q\} + \xi^2(\xi_B^o + k_B)}{(Q)^2 + \delta^2(\xi_B^o + k_B)^2} \quad (6)$$

$$Q = \xi_A^o\xi_B^o + \xi_A^o k_A + \xi_B^o k_B + \xi_B^o k_B/K$$

The symbols represent the following physical parameters:

a. ξ_A^o and ξ_B^o are the half-widths at half-height of a signal peak in a nonexchanging solution in system A and B, respectively.

b. V_B^o is the peak height of the signal in a nonexchanging solution at the frequency where the B system signal maximum appears, ignoring the small amount of signal due to the A system.

c. $M_Z^B\omega_1$ is $-\xi_B^o V_B^o$ at slow exchange assuming $\tau_B >> T_{2B}$.

d. Also, the product of the half width of a signal, ξ, and the height, V, approximate the area of the signal (9). Since the area is proportional to the concentration of the compound responsible for the signal and the concentration is independent of the hydrogen ion concentration in this study, the product, ξV should be constant.

To compensate for variations in the instrument an internal reference was added. A compound which would not be involved in the equilibrium, but which had an absorption peak near the peak being studied is

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9. E. Cremer and R. Muller, Mikrochim. Acta, 36/37, 553 (1951).

desirable. Therefore t-butyl alcohol was used, its nuclear magnetic resonance spectrum is a sharp singlet at 8.75τ in water.

If $\xi_B^o V_B^o$ is substituted for $M_Z^B \omega_1$ in Equation 6 and the left-hand side is multiplied and divided by the height of the reference peak, V_r, the resulting expression, Equation 7, gives the first-order rate constant for hydration-dehydration in terms of quantities that are independent of the rate of hydration-dehydration and the V_B.

$$\frac{V_B/V_R}{\xi_B^o V_B^o/V_R} = \frac{\{[\xi_A^o + k_B(1+1/K)] + [\xi_B^o + k_B(1+1/K)]K\}\{Q\} + \delta^2(\xi_B^o + k_B)}{(Q)^2 + \delta^2(\xi_B^o + k_B)^2} \qquad (7)$$

As a sidelight the degree of hydration of isobutyraldehyde was determined since the value was needed for the rate study. Lombardi and Sogo (10) examined the spectra of acetaldehyde and isobutyraldehyde in water but did not give the values of the hydration equilibrium constants. Nuclear magnetic resonance techniques permit the direct measurement of the values needed to calculate the equilibrium constant.

Several workers have used ultraviolet techniques to determine the degree of hydration of carbonyl compounds. However, to use this technique it is necessary to have a value for the extinction coefficient of the aldehyde in water. Various techniques have been employed to approximate the value.

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10. E. Lombardi and P. B. Sogo, J. Chem. Phys., 32, 635 (1960).

Rumpf and Bloch (11) have assumed the extinction coefficient of an aldehyde in water is equal to the product of the extinction coefficient of a reference ketone in water and the extinction coefficient of the aldehyde in dioxane, an inert solvent, divided by the extinction coefficient of the ketone in dioxane. Using 3-methyl-2-butanone as the reference ketone, Rumpf and Bloch found a value of 0.719 for the equilibrium constant, K. The temperature was not reported but other work from the same laboratory was reported at 20°.

Gruen and McTigue (1) have reported values for the equilibrium constant obtained from ultraviolet measurements in which the extinction coefficient of the isobutyraldehyde was determined by using a value that would give the best plot of log K versus 1/T. They reported a value of 0.44 for the equilibrium constant at 25°. They also reported a value of 7.3 kcal/mole for the enthalpy of hydration.

Herold (12) studied the hydration equilibrium in water using the extinction coefficient of isobutyraldehyde in an inert solvent as the actual coefficient in water. The temperature was not reported, but other workers in the same laboratory studied carbonyl hydration equilibrium at 18°. He reported a value of 0.92 for the equilibrium constant.

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11. P. Rumpf and C. Bloch, Compt. rend., 233, 1364 (1951).

12. W. Herold, Z. Physik. Chem., 18B, 265 (1932).

CHAPTER II

EXPERIMENTAL

The materials and equipment used for the experiments in this study are all described in Part II of this thesis. The acid solutions (perchloric acid in all cases) were standardized by normal techniques.

Nuclear Magnetic Resonance Spectra of Isobutyraldehyde

The nuclear magnetic resonance spectrum was examined neat and in water. The spectrum of the neat sample, Figure 1, consisted of three signals, a doublet at 8.93τ (J = 6.9 c.p.s.) due to the six methyl hydrogens split by the alpha hydrogen, a multiplet (7 split peaks) at 7.67τ (7.0 c.p.s.) assigned to the alpha hydrogen, and a doublet at 0.58τ (J = 1.1 c.p.s.) attributed to the aldehyde hydrogen. Tetramethylsilane was used as an internal reference. Ranft (13) reports values of 8.94τ (J = 7.0 c.p.s.) for the methyl doublet, 7.61τ for the multiplet and 0.43τ (J = 1.1 c.p.s.) for the aldehyde doublet. These values are in satisfactory agreement with the values found here.

In water or heavy water the spectrum, Figure 2, was complicated further by the hydrate peaks. The free aldehyde peaks were a doublet at 8.91τ (J = 6.9 c.p.s.), a multiplet at 7.44τ (J = 7 c.p.s.), and a doublet at 0.43τ (J = 1.5 c.p.s.). The peaks are assigned to the six methyl hydrogens, the alpha hydrogen and the aldehyde hydrogen, respectively.

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13. J. Ranft, Ann. Physik., 10, 1 (1962).

The hydrate spectrum consisted of a doublet at 9.07τ (J = 6.8 c.p.s.) assigned to the six methyl hydrogens, a multiplet (7 split peaks) at 8.32τ (J ≃ 7 c.p.s.) assigned to the alpha hydrogen and a doublet with one peak at 5.21τ, so close to the water peak that the other peak was believed to be in the water peak, assigned to the dihydroxymethyl hydrogen. The internal reference in this case was sodium 3-(trimethylsilyl)-1-propanesulfonate. In all cases the value of the coupling constant, J, was determined at 50 c.p.s. sweep width by measuring the distance in c.p.s. between the peaks in a group.

Attempts to Determine the Rate of Hydration of Isobutyraldehyde

Two attempts were made to determine the rate of hydration by direct observation of a change in a physical property of the aldehyde. The first attempt was the observation of the change in nuclear magnetic resonance spectrum with time. Small quantities of pure isobutyraldehyde were injected into nuclear magnetic resonance sample tubes containing water. The rate of hydration was too rapid to observe since it was necessary to shake the small n.m.r. sample tube several times to insure good mixing.

The second attempt was more successful. Using the peak in the ultraviolet at 285 mμ samples of isobutyraldehyde in water were studied. At 26°, 0.01 ml. of isobutyraldehyde was injected into 2 ml. of distilled water. The half-time of the reaction was determined by extrapolating the change in absorbance at 285 mμ back to zero time. The half-time was 12 seconds. Attempts were also made to examine the half-time at 7.8°, but the temperature of the reacting solution rose too rapidly for reliable measurements.

Nuclear Magnetic Resonance Determination of First-Order Rate Constant for Hydration

The study of the rate of the hydrogen ion catalyzed hydration of isobutyraldehyde was made using the equations described in the introduction. The experimental technique consisted of injecting 0.50 ml. samples of 3 per cent aqueous isobutyraldehyde solution into 0.25 ml. samples of perchloric acid in an n.m.r. sample tube filled with nitrogen. The various concentrations of perchloric acid were prepared from a standardized stock solution of 1.707 M perchloric acid by diluting with distilled water. The 3 per cent aqueous isobutyraldehyde solutions were prepared by syringing 0.32 ml. of isobutyraldehyde in 10 ml. of distilled water under nitrogen. Into this solution 0.02 ml. of t-butyl alcohol was added as an internal reference. The determination of the isobutyric acid concentration was made by sampling the stock 3 per cent solution and titrating with sodium hydroxide using bromothymol blue as an indicator. The concentration is indicated with each set of data.

Experimentally, it was not possible to reduce the concentration of acid in the reaction solutions to such a level that the hydration-dehydration rate was negligible. In all cases, the isobutyraldehyde solution contained small amounts of isobutyric acid.

To approximate the parameters in Equation 7 under nonexchange conditions, the following technique was used:

First, the water-catalyzed term was assumed to be no larger than ten times the uncatalyzed first-order rate of hydration at 25° (0.057 $sec.^{-1}$. For a lower limit the value of k_B^1, 0.005 was used. This value is lower than the value of 0.007 found for the uncatalyzed

term in the hydration of acetaldehyde at 25°.

Second, the ratio of ξ_A°/ξ_B° was assumed to be equal to ξ_A^1/ξ_B^1, a superscript 1 will be used to indicate parameters that have been measured under the lowest accessible acid concentrations. This assumption was checked at various low acid concentrations and found to hold reasonably well. This assumption is needed to determine a value for ξ_A° in terms of ξ_B° and parameters obtained at the lowest accessible acid concentration. Any error introduced by this assumption should be greatly minimized by the fact that the value of the term in which ξ_A° appears will be almost negligible under any circumstance.

Third, ξ_A° was replaced by $\xi_B^\circ\xi_A^1/\xi_B^1$ in Equation 7. Then substitute experimental values of the hydration equilibrium constant (0.423); the value of δ for the particular experiment; and the values for ξ_B^1, and V_B^1 at the lowest accessible acid concentration into Equation 7. These substitutions give an equation in two unknowns, ξ_B° and k_B. However, k_B has limits, $0 < k_B < 0.50$.

For values of 0.005, 0.05, 0.1, 0.2 and 0.5 for k_B^1 in the equation, values of ξ_B° and $V^\circ(\xi_B^\circ V_B^\circ = \xi_B^1 V_B^1)$ were obtained. Using these values of ξ_B° and V_B° in Equation 7, values of k_B were obtained at various acid concentrations. In all cases the second-order rate of acid-catalyzed hydration was the same. It would seem that any value of k_B^1 between 0.005 and 0.5 can be used to determine a set of ξ_B° and V_B° values without changing the value obtained for the second-order rate constant.

In all cases studied the isobutyraldehyde concentration was 2 per cent. The hydrogen ion concentration was corrected in all cases for the isobutyric acid in the aldehyde solutions. Tables 1, 2, and 3 contain

the experimentally observed values for the peak heights of the first aldehyde peak, B, at 68 c.p.s. and the reference compound peak at 75 c.p.s. Also listed are the value of the half-width at the half-height of the aldehyde peak, ξ_B^1 when no acid has been added. The results of this study are recorded in Table 5.

Table 1. Nuclear Magnetic Resonance Data for Acid Catalyzed Hydration

$\xi_B^1 = 0.40$ $V_B^1 = 18.05$ $\xi_B^o = 0.32$ $V_B^o = 22.55$

$\xi_A^1 = 0.63$ $V_{ref.} = 13.05$ $\xi_A^o = 0.50$ $V_{ref.} = 13.05$

$\delta = 12.00$

Acid Concentration x 10^4	V_B cm.	$V_{ref.}$ cm.
9.33	15.70	12.00
17.17	14.35	12.00
25.80	13.70	14.20
28.50	12.55	13.50
34.40	11.80	14.00
45.80	10.20	13.40

Table 2. Nuclear Magnetic Resonance Data for Acid-Catalyzed Hydration

$\xi_B^1 = 0.35$ $V_B^1 = 21.20$ $\xi_B^o = 0.27$ $V_B^o = 27.48$

$\xi^1 = 0.55$ $V_{ref.} = 14.20$ $\xi_A^o = 0.42$ $V_{ref.} = 14.20$

$\delta = 12.00$

Acid Concentration x 10^4	V_B cm.	$V_{ref.}$ cm.
4.74	20.35	15.81
9.33	19.80	14.85
17.17	17.00	13.80
25.80	16.50	16.75
28.50	14.90	15.80
34.40	14.45	15.90
45.80	13.02	16.00
51.20	12.00	15.70
57.30	12.30	16.60

Table 3. Nuclear Magnetic Resonance Data for Acid-Catalyzed Hydration

$\xi_A^1 = 0.55$ $V_B = 20.80$ $\xi_A^o = 0.44$ $V_B^o = 26.00$

$\xi_B^1 = 0.40$ $V_{ref.} = 11.60$ $\xi_B^o = 0.32$ $V_{ref.} = 11.60$

$\delta = 11.60$

Acid Concentration x 10^4	V_B cm.	$V_{ref.}$ cm.
28.6	13.6	11.1
34.3	14.3	12.3
45.8	10.8	11.0
51.5	10.2	11.0
52.2	10.2	11.5

Equilibrium Constant for Isobutyraldehyde-Isobutyraldehyde Hydrate in Water

The equilibrium constant for the hydration of isobutyraldehyde was determined in two ways from the nuclear magnetic resonance spectra of an aqueous solution of isobutyraldehyde. The only experimental work needed was preparing a 5 per cent isobutyraldehyde solution in distilled water and examining its spectrum.

As has been previously mentioned the peaks due to the six methyl hydrogens of the hydrate appear 11 c.p.s. upfield from the signal for the same protons of the free isobutyraldehyde. The relative magnitude of the signals can be determined by integrating the four peaks involved

or determining the area of the signal. The temperature of the nuclear magnetic resonance spectrometer probe was determined with the special thermometer described in Part II. The area under the curve was determined by measuring the peak height and the width of the peak at half-height (9). Since the nuclear magnetic resonance spectrometer is equipped with a variable-temperature probe the equilibrium constant was obtained at both 25° and 35°, the two temperatures used in this work. The temperature of the probe was calibrated at 25° with ethylene glycol as described by the Varian Company. The spectrum is integrated at each temperature every few minutes for 30 minutes to insure that the sample has reached equilibrium. Table 4 contains the experimental data obtained.

Table 4. Equilibrium Constant for the Hydration of Isobutyraldehyde in Aqueous Solution

Time (Minutes)	Isobutyraldehyde[a]	Isobutyraldehyde Hydrate[b]
	25°	
15	25.00	15.00
15	24.00	14.30
30	24.50	15.25
30	24.75	15.25
45	24.50	14.75
45	24.00	14.50
60	24.75	14.75
60	24.75	14.75
	35°	
15	26.00	11.00
15	26.00	11.00
30	26.00	11.00
30	26.00	11.00

[a] Area of the doublet due to the methyl groups of isobutyraldehyde.

[b] Area of the doublet due to the methyl groups of isobutyraldehyde hydrate.

CHAPTER III

RESULTS AND DISCUSSION

To obtain values in conventional units for the first-order rate constant for the hydration of isobutyraldehyde from the values of k_B calculated from Equation 7, it is necessary to multiply the value of k_B by 2π. This becomes necessary because the term, ξ, is obtained from the width of the nuclear magnetic resonance signal. This measurement is usually made in cycles per seconds in nuclear magnetic resonance spectrometry. The factor of 2π is needed to convert cycles to radians which are unitless. When k_B is multiplied by 2π, the resulting rate constant has the more conventional units of seconds^{-1}.

The rate of acid-catalyzed hydration of isobutyraldehyde has been measured by nuclear magnetic resonance spectrometry using a line-broadening technique. The technique is described in the Introduction. The individual values obtained for the second order rate constant for acid-catalyzed hydration are in Table 5. The average second-order rate constant is 442 l.-m.$^{-1}$-sec.$^{-1}$. The value is larger than the value, 370 l.-m.$^{-1}$-sec.$^{-1}$, reported by Gruen and McTigue (1) at 25° using a calorimetric technique. They also reported the value of the second-order rate constant for the acid-catalyzed hydration of acetaldehyde at 25° to be 800 l.-m.$^{-1}$-sec.$^{-1}$ which is in reasonable agreement with the values

Table 5. Second Order-Rate Constants for Acid-Catalyzed Hydration of Isobutyraldehyde

Ex-94	$k_{obs.}$	$k_{H+}[H^+]sec.^{-1}$	k_{H+} l.-m.$^{-1}$sec.$^{-1}$
2.86	0.269	1.20	415
3.43	0.306	1.42	414
4.58	0.421	2.14	469
5.15	0.466	2.42	470
5.72	0.502	2.65	463
Ex-98-40			
0.93	0.101	0.13	18.8
1.72	0.140	0.38	31.4
2.58	0.254	1.09	423
2.85	0.275	1.22	430
3.44	0.338	1.62	471
4.58	0.411	2.08	443
Ex-98-50			
0.47	0.142	0.39	823
0.93	0.127	0.30	314
1.72	0.161	0.51	295
2.58	0.269	1.19	460
2.85	0.293	1.34	469
3.44	0.314	1.47	427
4.58	0.383	1.90	416

Table 5. Second Order-Rate Constants for Acid-Catalyzed Hydration of Isobutyraldehyde (Continued)

Ex-98-50	$k_{obs.}$	$k_{H+}[H^+]sec.^{-1}$	k_{H+} l.-m.$^{-1}$-sec.$^{-1}$
5.12	0.426	2.17	425
5.73	0.448	2.31	422 Avg 70.3 + 4.4

In determining the average value of k_{H+}, the values obtained for acid concentrations below 0.002 M were ignored because of the large deviation and the uncertainty in the acid concentrations.

reported by Bell and co-workers (14, 15) at 0° and 25° using the same technique.

From the values obtained by Bell and co-workers at 25° and 0°, the activation energy for the acid-catalyzed hydration is 17.6 kcal/mole. From this value of the activation energy the second-order rate constant for acid-catalyzed hydration of acetaldehyde is 1400 l.-m.$^{-1}$-sec.$^{-1}$ at 35°. Taft's E_s for the isopropyl group (0.47) indicated that nucleophilic attack on the isobutrate ester tends to occur only one-third as often as on the corresponding acetate ester. Using Bell's data for acetaldehyde, one might justify a value of 740 l.-m.$^{-1}$-sec.$^{-1}$ for the second-order

14. R. P. Bell and J. C. Clunie, Proc. Roy. Soc. (London), 212A, 33 (1952).

15. R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, Trans. Faraday Soc., 52, 1093 (1956).

rate constant for acid-catalyzed hydration of isobutyraldehyde.

The hydration equilibrium constant, K, has been determined in this work to be 0.604 at 25° and 0.423 at 35°. From these values the enthalpy of hydration is -6.5 kcal/mole. Gruen and McTigue reported values for the equilibrium constant that were some 40 per cent lower than those obtrained in this work; however, their value of -7.3 kcal/mole for the enthalpy of hydration is within experimental error of the value obtained in this work. The nuclear magnetic resonance technique allows the direct measurement of the hydrate and aldehyde. This eliminates some of the uncertainties involved in ultraviolet determinations.

CHAPTER IV

CONCLUSION

This work gives a two-fold indication of the usefulness of nuclear magnetic resonance techniques in kinetics and equilibrium studies. The technique provided a method for studying reactions which are quite fast. The equations developed by McConnell and used by Charman, Vinard and Kreevoy yield first-order rate constants for the hydration of isobutyraldehyde that agree with values obtained by calorimetric techniques. The hydration equilibrium constant can be determined from nuclear magnetic resonance data quite easily whereas ordinary techniques are very difficult to apply.

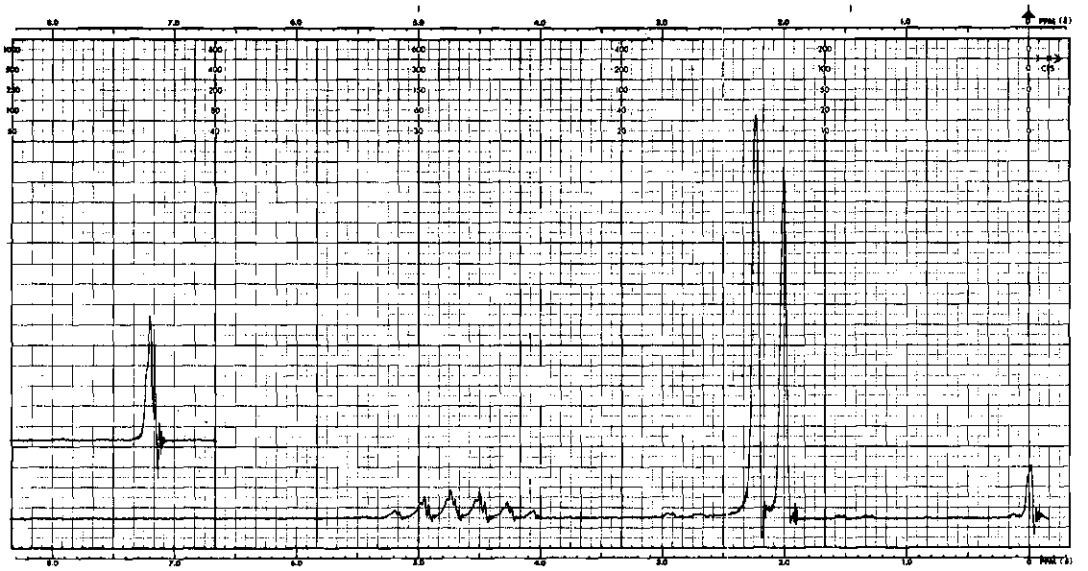

Figure 1. Nuclear Magnetic Resonance Spectrum of Isobutyraldehyde Neat. Sweep Time: 250 Seconds; Sweep Width: 250 c.p.s.; Insert Offset: 350 c.p.s.; Filter Bandwidth: 4 c.p.s.; R. F. Field: 0.02 mG.; Spectrum Amp.: 0.63.

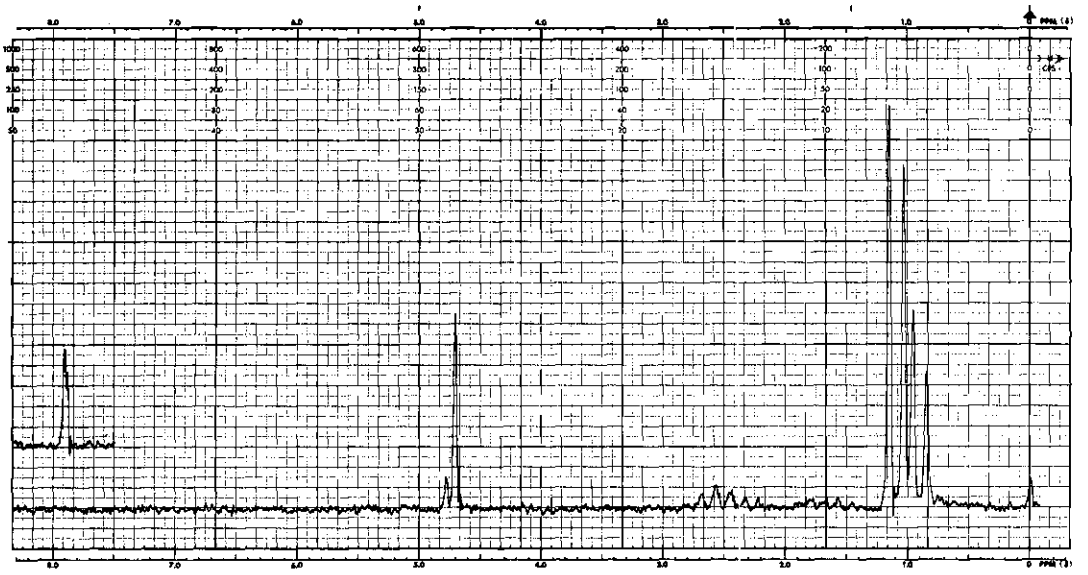

Figure 2. Nuclear Magnetic Resonance Spectrum of Isobutyraldehyde in Deuterium Oxide. Sweep Time: 250 Seconds; Sweep Width: 500 c.p.s.; Insert Offset: 100 c.p.s.; Filter Bandwidth: 1 c.p.s.; R. F. Field: 0.05 mG.; Spectrum Amp.: 12.5.

APPENDIX

LITERATURE CITED

1. L. C. Gruen and P. T. McTigue, *Journal of the Chemical Society, 1963,* 5224.

2. H. M. McConnell, *Journal of Chemical Physics, 28,* 430 (1958).

3. F. Bloch, *Physical Reviews, 70,* 460 (1946).

4. H. S. Gutowsky, D. W. McCall, and C. P. Slichter, *Journal of Chemical Physics, 21,* 279 (1953).

5. H. M. McConnell and S. B. Berger, *ibid., 27,* 230 (1957).

6. E. Grunwald, A. Loewenstein and S. Meiboom, *ibid., 27,* 630 (1957).

7. H. S. Gutowsky and A. Saika, *ibid., 21,* 1688 (1953).

8. H. B. Charman, D. R. Vinard and M. M. Kreevoy, *Journal of the American Chemical Society, 84,* 347 (1962).

9. E. Cremer and R. Muller, *Mikrochimica Acta, 36/37,* 553 (1951).

10. E. Lombardi and P. B. Sogo, *Journal of Chemical Physics, 32,* 635 (1960).

11. P. Rumpf and C. Bloch, *Comptes Rendus, 233,* 1364 (1951).

12. W. Herold, *Zeitschrift fuer Physikalische Chemie, 18B,* 265 (1932).

13. J. Ranft, *Annalen der Physik, 10,* 1 (1962).

14. R. P. Bell and J. C. Clunie, *Proceedings of the Royal Society* (London), *212A,* 33 (1952).

15. R. P. Bell, M. H. Rand and K. M. A. Wynne-Jones, *Transactions of the Faraday Society, 52,* 1093 (1956).

PART TWO

CHAPTER I

INTRODUCTION

The extraordinary catalytic activity of enzymes has been ascribed to the ability of the active sites of the enzyme to perform their various catalytic functions simultaneously, or nearly so, on the substrate (1). It would seem for reactions consisting of several steps, organic molecules with various different functional groups similar to the active sites of an enzyme could simulate the catalytic action of an enzyme. Swain and Brown (1) reported the first example of "enzyme-like" or polyfunctional catalysis by a simple organic molecule. They found in the mutarotation of tetramethylglucose that 0.001 M 2-hydroxypyridine was 7,000 times as effective a catalyst as a mixture of 0.001 M pyridine and 0.001 M phenol. Yet 2-hydroxypyridine has an acid strength one-hundredth that of phenol and a base strength only one ten-thousandth that of pyridine. The rate enhancement is explained in terms of polyfunctional catalysis.

Westheimer and Cohen (2) found that the dealdolization of diacetone alcohol was catalyzed by primary and secondary amines but not by

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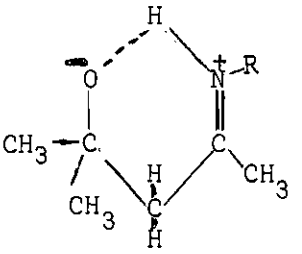
1. C. G. Swain and J. F. Brown, Jr., J. Am. Chem. Soc., 74, 2534 (1952).

2. F. H. Westheimer and H. Cohen, J. Am. Chem. Soc., 60, 90 (1938).

tertiary amines. Westheimer (3) later proposed a cyclic intermediate with an imine linkage to account for this observation. Enzymes may function in a similar fashion



(1)

by having active sites on their surface which can provide a primary or secondary amine end-group to form an electron withdrawing imine linkage with a carbonyl group and a tertiary amine or some other basic group to remove a proton. Thus, an enzyme could "engulf" the molecule and all the steps in a reaction could proceed in an almost concerted manner.

This research was concerned for the most part with deuterium removal by tertiary amines and phenoxide ions. To study this process the system isobutyraldehyde in water was chosen. The system has several good and some bad points. The aldehyde is oxidized quite easily and must be handled with care in an inert atmosphere. Isobutyraldehyde is soluble to the extent of only 8 to 10 per cent in water. This means that in the dilute solutions used the signal to noise ratio will be unfavorable at times for nuclear magnetic resonance spectrometry. A further complica-

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3. F. H. Westheimer, Ann. N. Y. Acad. Sci., 39 (Art 5), 401 (1940).

tion is the aldol condensation that occurs if the aldehyde and the base become too concentrated. The hydroxide ion must also be kept below 0.003 M to keep the hydration-dehydration equilibrium from being too rapid to follow the kinetics with nuclear magnetic resonance.

Despite these minor difficulties the system has several advantages. The deuterium exchange of isobutyraldehyde-2-d in water can be followed with nuclear magnetic resonance spectrometry. Isobutyraldehyde has only one exchangeable hydrogen thus eliminating the statistical problems involved with things like partially deuterated acetone. The nuclear magnetic resonance spectrum of a mixture of isobutyraldehyde and isobutyraldehyde-2-d is simple and the α-methyl groups of the mixture give a clean five peak spectrum consisting of a doublet from isobutyraldehyde surrounding three interior peaks from isobutyraldehyde-2-d. This allows the α-methyl group spectrum to be swept in ten seconds at fifty-second sweep width. The isobutyraldehyde-2-d is easily prepared. Water was used as a solvent for the kinetic studies to approximate the environment in which normal enzymatic catalysis occurs.

Before considering various polyfunctional models, it seemed reasonable to examine the various functional groups that could be used as catalysts to determine the best type of "active sites" to put on the polyfunctional catalyst. That is to say that not only must the "active sites" be sterically in the correct position, but they must also have the ability to do the job assigned them. In accord with this idea, we have studied various catalysts which could not form imine linkages, but could function in a proton removal step. The deuterium exchange study involved a survey of the use of various tertiary amines and oxygen bases

as catalysts for the exchange of isobutyraldehyde-2-d.

The nitrogen bases considered were of two types, the pyridine bases and alkyl tertiary amines. Tertiary amines were chosen because they cannot participate in the formation of an enamine with the carbonyl group. To study the effect of hindrance, amines with two of the alkyl groups back in a ring were used and in one case all three alkyl groups were held back in a bicyclic compound. The simple alkyl amines had varying degrees of hindrance.

One area that would seem to be pertinent to our study is the base-catalyzed halogenation of ketones. For many years it has been known that the rate-determining step in this reaction is the proton-removal step (4, 5). A correlation of the ability of a series of bases to remove a proton is the Bronsted equation (6). The Bronsted Equation,

$$k_B = GK_B^X$$

where k_B is the catalytic constant for any base B, and K_B is its ionization constant; G is a constant for a series of similar bases and X is between zero and one, and relates the base strength and the catalytic activity.

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4. J. Hine, Physical Organic Chemistry, 2nd ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, sec. 5-2B.

5. R. P. Bell, The Proton in Chemistry, Cornell University Press, Ithaca, N. Y., 1959, p. 143.

6. J. N. Bronsted, Chem. Rev., 5, 231 (1928).

Pearson and Williams (7, 8) examined the base-catalyzed iodination of nitroethane. Even though the substrate in this system is not very hindered, they found that some bases were less effective catalysts in the rate-determining ionization of the nitroethane than would be expected from their base strength. They found that 2,6-dimethylpyridine, 2,4,6-trimethylpyridine and 2-methylquinoline had catalytic constants that were low compared to those of a series of pyridines and quinolines. They noted that a single substituent in the 2 position of pyridine did not slow the rate. This might well be due to the fact that the hydrogen being removed is not surrounded by bulky groups.

Lewis and Allen (9) have studied the iodination of 2-nitropropane and nitroethane catalyzed by 2- and 2,6-substituted pyridines in 30 per cent ethanol. They found in the protium exchange that the pyridine-catalyzed iodination of 2-nitropropane occurs at about the same rate as the 2,6-lutidine-catalyzed reaction even though 2,6-lutidine is more basic. The 2-t-butylpyridine-catalyzed iodination is only 1/16 as fast as the pyridine-catalyzed iodination. Steric effects in the pyridine-catalyzed iodination of nitroethane were much smaller if they were present at all.

Feather and Gold (10) have studied the base-catalyzed iodination

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7. R. G. Pearson and F. V. Williams, J. Am. Chem. Soc., 75, 3073 (1953).

8. R. G. Pearson and F. V. Williams, ibid., 76, 258 (1954).

9. E. S. Lewis and J. D. Allen, J. Am. Chem. Soc., 86, 2022 (1964).

10. J. A. Feather and V. Gold, Proc. Chem. Soc., 1962, 306.

of a series of ketones with various alkyl groups attached to the alpha carbon. As bases they used a group of hindered and unhindered pyridines. The conclusions drawn were that the pyridines substituted in the 2 and 2,6 positions were abnormally slow as was indicated by a Bronsted plot of both the hindered and unhindered bases. However, the workers did not indicate if the products were analyzed to see which proton was removed. Since the ketones studied were formulated RCH_2COR' and the hindered group was introduced via R' and R' was methyl in three of the five cases studied, it would seem that the least hindered proton would be removed for steric and electronic reasons. The case cited as the one showing the largest effect, cyclohexanone--2,4,6-trimethylpyridine, might be due to the miscalculation of a statistical factor. The conformation of the cyclohexane ring leaves a question as to the number of hydrogens that can be removed.

Bell and Wilson (11) found no deviations from a Bronsted treatment when they studied the base-catalyzed decomposition of nitramide in water and anisole.

$$HN = NO_2H + B \rightleftarrows BH^+ + N_2O + OH^-$$

They used a series of pyridines including 2-methylpyridine, but no 2,6- or 2,4,6- substituted pyridines. From these data it would appear that to show marked hindrance the proton being removed must have some bulky groups around it.

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11. R. P. Bell and G. T. Wilson, Trans. Faraday Soc., 46, 407 (1950).

Another reaction involving proton removal as the rate-determining step is the hydration of aldehydes and ketones. Bell, Rand, and Wynne-Jones (12) indicate in their study of the base-catalyzed hydration of acetaldehyde that the 2- and 2,6- substituted pyridines have abnormally low catalytic constants compared to the other substituted pyridines. The effect is not large, but acetaldehyde is not very hindered.

In a comprehensive study of a large number of bases Bell and Jensen (13) examined the base-catalyzed hydration of sym-dichloroacetone. They found that hydration catalyzed by pyridines substituted in the 2- and 2,6- positions occurs at a slower rate than would be expected from a Bronsted plot of the substituted pyridines. They also observed that the charged bases were some 1,000 times better catalysts than the uncharged bases.

Westheimer and Covitz (14) found in three cases that pyridines substituted 2,6- and 2,4,6- were markedly hindered. The cases considered were: the hydrolysis of methyl ethylene phosphate, the mutarotation of glucose and the inversion of (-) menthone. The studies were made in 70 per cent ethanol.

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12. R. P. Bell, M. H. Rand and K. M. A. Wynne-Jones, Trans. Faraday Soc., 52, 1093 (1956).

13. R. P. Bell and M. B. Jensen, Proc. Roy. Soc. (London), A261, 38 (1961).

14. F. H. Westheimer and F. Covitz, J. Am. Chem. Soc., 85, 1773 (1963).

Gold (15) discusses steric hindrance of proton removal in acid-base reactions and in equilibria that involve proton transfers. He feels that proton removal can be hindered but not to a large extent. It would seem, however, that no one has ever reported the study of a system in which both substrate and catalyst are highly hindered.

Another reaction that may give some understanding of the mechanism of the exchange of protons alpha to a carbonyl group by amines is the decarboxylation of β-keto acids. Pedersen (16) found that the decarboxylation of acetoacetic acid is catalyzed by aniline. He later found that the decarboxylation was not general base catalyzed but is specifically primary amine catalyzed (17). He suggested that the amine catalysis is due to the formation of a Schiff base as an intermediate:

$$> C = O + H_2NR \rightleftarrows > C = NR + H_2O$$

The C = NR group would have stronger basic properties than the keto group. Other workers (18, 19) have found that the decarboxylation of β-keto-acids is slightly catalyzed by tertiary and secondary amines but primary

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15. V. Gold, Progress in Stereochemistry, Vol. 3, Butterworths, London, 1962, p. 169.

16. K. J. Pedersen, J. Phys. Chem., 38, 559 (1934).

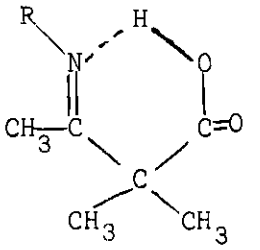
17. Idem., J. Am. Chem. Soc., 60, 595 (1938).

18. E. O. Wiig, J. Phys. Chem., 32, 961 (1928).

19. W. Franke and G. Brathuhn, Ann., 487, 1 (1931).

amines increase the rate to a much greater extent.

Westheimer and Jones have studied the rate of decarboxylation of α,α-dimethylacetoacetic acid in various solvents (20). They found that the rate of decarboxylation is virtually independent of the dielectric constant of the solvent over the range studied. This would eliminate a zwitterion type Schiff-base intermediate and suggest a cyclic ketimine intermediate like the one suggested by Westheimer (2) for the dealdolization of diacetone alcohol.



Matsumoto (21) has studied the decarboxylation of acetoacetic acid in various solvents with aminoantipyrine. He also suggests the formation of a ketimine intermediate.

Of interest to the idea of polyfunctional catalysis and enzymes, Westheimer and Fridovich have found that the decarboxylation of acetoacetic acid by the decarboxylase from Cl. acetobutylicum proceeds by way

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20. F. H. Westheimer and W. A. Jones, J. Am. Chem. Soc., 63, 3283 (1941).

21. S. Matsumoto, Tech. Bull. kagawa Agr. Coll. (Japan) 5, 103 (1953); C. A., 49, 7493i(1955).

of a Schiff base or a Schiff-base salt (22).

In the isobutyraldehyde-base system one of the interesting and necessary data needed is the equilibrium constant for the aldehyde-aldol equilibrium. Usherwood (23) studied the equilibrium and reported in heterogenous equilibrium at 35° there is 10 per cent aldehyde and 90 per cent aldol present. At the time of this work the trimer was not well defined. From the boiling points and the reaction conditions it appears that Usherwood was studying the trimer formation and decomposition.

In a polyfunctional acid-base catalyst both an acid "site" and a base "site" are required. In normal catalysis this would be the same as adding both an acid and a base to the reaction as Swain and Brown (1) did in the case of the mutarotation of tetramethylglucose. Some reactions may fall in the category of termolecular reactions with the solvent acting as one component.

Shilov and Yasnikov (24) studied the iodination of acetone at various pH's and with various amino acids. They propose that at certain pH's there are termolecular terms involving the acetone, a basic group and an acidic group. The acidic and basic functional groups can be provided by the amino acid or the buffer. However, they also reported terms that have only a single amino acid component implying the formation of

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22. F. H. Westheimer and I. Fridovich, J. Am. Chem. Soc., 84, 3208 (1962).

23. E. H. Usherwood, J. Chem. Soc., 123, 1717 (1923).

24. E. A. Shilov and A. A. Yasnikov, Ukrain. Khim. Zhur., 27, 639 (1961).

a cyclic ketimine-type intermediate.

It would seem, then, that the study of the proton exchange in isobutyraldehyde will provide a system that can be used to study several problems. The substrate is hindered enough to provide a study of the hindrance in proton removal. The system lends itself to the study of polyfunctional catalysts in an acid-base system.

CHAPTER II

EXPERIMENTAL RESULTS

Chemicals[1]

Acetic Acid--Baker Analyzed reagent grade acetic acid was used without further purification.

o-Chlorophenol--Fisher Scientific Company o-chlorophenol was distilled under nitrogen using column No. 1.[2]

m-Chlorophenol--Eastman white label m-chlorophenol was distilled under nitrogen using column No. 2.[2]

p-Chlorophenol--Eastman white label p-chlorophenol was vacuum-sublimed at approximately five mm. and 125°.

o-Cresol--Eastman practical grade o-cresol was distilled under nitrogen using column No. 1.

p-Cresol--Eastman practical grade p-cresol was distilled under nitrogen using column No. 3.[2]

Dimethylaminoethanol--Stock dimethylaminoethanol was distilled under nitrogen using column No. 3.

Isobutyraldehyde--Eastman Chemical Company supplied a sample of isobutyraldehyde which was distilled under nitrogen using column No. 3.

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[1] The boiling and melting points that were determined are listed in Tables 1 and 2 at the end of this section.

[2] The columns are discussed in the section on equipment.

Imidazole--Eastman white label imidazole was used without further purification.

2,4-Lutidine--Aldrich Chemical Company 2,4-lutidine was distilled under nitrogen using column No. 3.

2,6-Lutidine--Eastman white label 2,6-lutidine was used without further purification after gas-liquid chromotography[3] using column A[2] and column K[2] indicated no impurities.

3,4-Lutidine--Aldrich Chemical Company reagent grade 3,4-lutidine was distilled under nitrogen using Column No. 2.

Methylamine Hydrochloride--Eastman white label methylamine hydrochloride was used without further purification.

N-Methyldiethylamine--Eastman white label N-methyldiethylamine was used without further purification after g. l. c. using Column A and Column K showed no impurities.

N-Methylmorpholine--Carbide and Carbon Chemical Company reagent grade N-methylmorpholine was distilled under nitrogen using Column No. 3.

N-Methylpiperidine--Aldrich Chemical Company N-methylpiperidine was distilled under nitrogen using Column No. 2.

N-Methylpyrrolidine--Aldrich Chemical Company N-methylpyrrolidine was distilled under nitrogen using Column No. 2.

m-Nitrophenol--Eastman white label m-nitrophenol was vacuum-sublimed at approximately 10 mm. and 125°.

p-Nitrophenol--Eastman white label p-nitrophenol was vacuum-sublimed at 10 mm. and 125°.

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[3] In the following discussions the abbreviation g. l. c. will be used.

Perchloric Acid--Baker Analyzed reagent grade perchloric acid was used without further purification.

Phenol--Baker Analyzed reagent grade phenol was distilled under nitrogen using Column No. 2. A yellow color appeared when the buffer was prepared. To check the purity further a sample of phenol was vacuum-sublimed at 10 mm. The buffer made from this material also has a slight yellow color.

4-Picoline--Aldrich Chemical Company 4-picoline was used without further purification after g. l. c. using Column A and Column K indicated no impurities.

2,2',2"- Nitrilotriethanol--Triethanolamine was obtained from Dr. Julien Mulders. The material had been distilled under reduced pressure using a vacuum-jacketed column containing glass helices.

Triethylamine--Eastman white label triethylamine was used without further purification after the nuclear magnetic resonance spectrum of an aqueous solution indicated no impurities.

1,4-Diazabicyclo[2.2.2.]octane--Houdry Process Corporation 1,4-diazabicyclo [2.2.2]octane was used without further purification.

Trimethylamine--Eastman white label trimethylamine was used without further purification.

Trimethylamine-N-oxide--Trimethylamine-N-oxide was prepared by Dr. Jack Hine by the oxidation of trimethylamine with hydrogen peroxide and vacuum-sublimed.

2,4,6,-Trimethylpyridine--Eastman white label 2,4,6-trimethylpyridine was used without further purification after g. l. c. using Column A and Column K indicated no impurities.

Sodium Perchlorate--G. Frederick Smith Chemical Company reagent grade sodium perchlorate was used without further purification.

Synthesis of Isobutyraldehyde-2-d--The first attempt to make isobutyraldehyde-2-d was to reflux isobutyraldehyde in heavy water using sodium carbonate as a catalyst. The refluxing system was flushed for some time with nitrogen and 4.26 g. (0.04 mole) of sodium carbonate was added to a mixture of 20 ml. of heavy water and 20 ml. (0.22 mole) of isobutyraldehyde. After mixing the liquid became warm and more viscous than either component. The mixture was refluxed four and one-half hours and a white solid material formed in the flask. The temperature was raised to distill the products. The distillate proved to be heavy water. The white solid material was believed to be a condensation product of isobutyraldehyde. This synthetic route was abandoned without further examination.

The second attempt to prepare isobutyraldehyde-2-d involved the use of a trimethylamine-trimethylammonium perchlorate buffer to catalyze the exchange in heavy water. To 100 ml. of heavy water, 26 ml. of a buffer composed of 2.08 M trimethylamine and 0.69 M trimethylammonium perchlorate prepared in heavy water was added. This solution was poured into a 250 ml. separatory funnel along with 4 ml. of isobutyraldehyde and shaken for several minutes. The solution became cloudy almost at once. After standing for approximately one hour, the mixture was extracted with three 20-ml. portions of m-xylene.

In order to determine if the m-xylene solutions of isobutyraldehyde-2-d could be washed with 1 M hydrochloric acid and water without loss of deuterium, 25 ml. of the m-xylene solution was divided into

two 12.5-ml. portions. One 12.5-ml. portion was washed with 10 ml. of 1 M deuterium chloride in heavy water and then with two 10-ml. portions of heavy water. The second 12.5-ml. portion was washed with 10 ml. of 1 M hydrochloric acid and then with two 10-ml. portions of water. Both m-xylene solutions, after drying over silca gel, gave identical nuclear magnetic resonance spectrum.

The three m-xylene extracts were poured together and washed with two 15-ml. portions of 1 M hydrochloric acid followed by three 20-ml. portions of water. The m-xylene solution was then dried over silca gel for ten minutes and stored under nitrogen. The procedure was repeated several times until approximately 250 ml. of combined m-xylene solution was obtained. After each set of three extractions enough buffer was added to account for the amount of trimethylamine removed. This usually amounted to 10 to 12 ml. of the buffer. The m-xylene solution was distilled under nitrogen on Column No. 3.

In a normal preparation the procedure was repeated five times. The yields of isobutyraldehyde-2-d were approximately 33 per cent. The purity of the material was indicated by its typical nuclear magnetic resonance spectrum, refractive index and boiling point. The refractive index was 1.3750 at 19° and the boiling point was 63-63.5°. The nuclear magnetic resonance spectra, Figures 8, 9 and 10, were clean and indicated only the expected peaks,

The nuclear magnetic resonance spectrum of isobutyraldehyde-2-d neat consists of a triplet (6 protons) at 8.94τ (J = 1.05 c.p.s.) and a broad peak (one proton) at 0.57τ that could not be resolved. Tetramethylsilane was used as an internal standard. The 8.94τ triplet is at-

tributed to the six methyl hydrogens split by the deuterium and the 0.57τ broad peak is assigned to the aldehyde hydrogen. The value of J_H/J_D is 6.67 which is in agreement with the value of 6.55 predicted by Gutowsky, Karplus and Grant (25) from theoretical considerations.

The spectrum in heavy water using sodium 3-(trimethylsilyl)-1-propanesulfonate as an internal standard consists of a triplet (6 protons) at 8.90τ (J = 1.05 c.p.s.), a broad peak (6 protons) at 9.09τ, a broad peak (1 proton) at 5.23τ and a broad peak (1 proton) at 0.43τ. The peaks that did not appear in the spectrum of the neat sample are attributed to the hydrate. The 9.09τ peak is assigned to the six methyl hydrogens and the peak at 5.23τ is assigned to the hydrogen on the dihydroxymethyl group.

During the later phases of the study the isobutyraldehyde-2-d was provided by Dr. Julien Mulders and Dr. Jack Hine. This material was prepared by hydrolysis of isobutenyl acetate in heavy water. In one lot of material synthesised in this manner there appeared to be an impurity that catalyzed the formation of the isobutyraldehyde trimer--2,4,6-triisopropyl-1,3,5-trioxane--which crystallized out of the pure isobutyraldehyde-2-d. When this occurred the isobutyraldehyde-2-d was redistilled to remove the trimer.

Synthesis of 2,6-Diisopropyl-5,5-dimethyl-4-m-Dioxanol--The procedure for the synthesis of 2,6-diisopropyl-5,5-dimethyl-4-m-dioxanol

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25. H. S. Gutowsky, M. Karplus and D. M. Grant, J. Chem. Phys., 31, 1278 (1959).

was similar to that described by Saunders, Murray, and Cleveland (26). To a precooled three-necked flask equipped with a stirrer, separatory funnel and thermometer was added 100 ml. of isobutyraldehyde, 100 ml. of diethyl ether and 15 drops of di-n-butylamine. This mixture was cooled to 4° and a 10 per cent by weight solution of potassium hydroxide was added at a rate that did not allow the temperature to exceed 10°. The reaction was considered complete when the addition of 10 ml. of potassium hydroxide did not caused the temperature to rise. The total amount of 10 per cent potassium hydroxide solution used was 80 ml.

The heterogeneous mixture was separated with a separatory funnel and the organic layer was washed three times with 25-ml. portions of distilled water. The organic layer was then dried over anhydrous sodium sulfate for four hours. The ether was removed at reduced pressure and the product distilled at 5 mm. The fractions distilling at 99-100° at 3 mm. were 2,6-diisopropyl-5,5-dimethyl-4-m-dioxanol. The yield was 64 g. or 80 per cent.

Attempted Synthesis of Isobutyraldol--Using the technique reported by Saunders, Murray and Cleveland (24), the synthesis of isobutyraldol was attempted. The diethyl ether solution obtained by the addition of 80 ml. of a 10 per cent potassium hydroxide solution to a mixture of one 100 ml. of isobutyraldehyde and one 100 ml. of diethyl ether at 0-10°C. was separated from the aqueous phase and washed with vigorous shaking with several 25-ml. portions of 5 per cent sulfuric acid. The organic layer was dried for several hours over anhydrous sodium sulfate. The

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26. R. H. Saunders, M. J. Murray and F. F. Cleveland, J. Am. Chem. Soc., 65, 1714 (1943).

diethyl ether was removed at reduced pressure and the product distilled at 2-3 mm. pressure. The product was collected at 99-100°C. The nuclear magnetic resonance spectrum indicated no aldehyde hydrogen peak in the region around 550 c.p.s. downfield from tetramethylsilane as expected for isobutyraldol.

Synthesis of Isobutyraldol (3-Hydroxy-2,2,4-trimethylvaleraldehyde)--A mixture of 13 grams of 2,6-diisopropyl-5,5-dimethyl-4-m-dioxanol and 50 ml. of water was refluxed with 5.5 ml. of 1 M sulfuric acid for several hours. The temperature was raised and the water-isobutyraldehyde azetrope was distilled at 72-99° on Column No. 2. The distillation was stopped when no more isobutyraldehyde was observed in the distillate. The pot residue was allowed to cool and was then extracted with 100 ml. of diethyl ether. The ether extract was dried for a few minutes over anhydrous sodium sulfate and the ether removed at reduced pressure. The organic residue was vacuum distilled at 70-75° at 3 mm. The yield was 2.4 g. or 27 per cent.

The nuclear magnetic resonance spectrum, Fig. 11 , of isobutyraldol in carbon tetrachloride consists of six protons in a doublet at 9.1τ (J = 6.8 c.p.s.) and a doublet at 9.07τ (J = 6.8 c.p.s.), six protons in a singlet at 8.93τ, one proton in a multiplet at 8.2τ, a singlet at 7.35τ, one proton in a doublet at 6.52τ (J = 4.0 c.p.s.) and one proton in a singlet at 0.50τ. The two doublets at 9.1τ and 9.07τ are assigned to the six hydrogens on the methyl groups on carbon four. The splitting is due to the asymmetric center at carbon three. The singlet at 8.93τ is attributed to the six hydrogens on the two methyl groups on carbon two which happens to be unsplit. The multiplet at

8.20τ is assigned to the hydrogen on carbon four. The singlet at 7.35τ is assigned to the hydrogen on the hydroxyl group. During the study the observation was made that the position of the hydroxyl group hydrogen was dependent on the concentration. The doublet at 6.52τ was assigned to the hydrogen on carbon three and the 0.50τ peak was assigned to the aldehyde hydrogen. Tetramethylsilane was used as an internal standard. In the neat spectrum of isobutyraldol the six protons on the methyl groups on carbon two are split into a doublet and the six protons on the methyl groups on carbon four are split into only one doublet.

The nuclear magnetic resonance spectrum of a saturated solution of isobutyraldol in heavy water, Fig. 12, consisted of singlets at 9.07τ, 9.17τ, 8.92τ and 0.42τ. At 8.15τ and 7.15τ there were blurred multiplets and at 6.49τ (J = 5 c.p.s.) a doublet. The doublets that appeared at 9.07τ and 9.1τ in carbon tetrachloride have merged into singlets at 9.07τ and 9.17τ. The other peaks have the same assignments as before with slight shifts. The internal reference in heavy water was sodium 3-(trimethylsilyl)-1-propanesulfonate.

In a symposium Hagemeyer and co-workers (27) reported similar results concerning the difficulty in obtaining the aldol from an acid wash as described by Saunders and co-workers (26). They found that the dioxanol in 1 per cent acetic acid at reflux gave 90 per cent yields of aldol. This technique was used on a small scale in this study and found to be very effective.

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27. H. J. Hagemeyer, G. V. Hudson, S. H. Johnson, M. B. Edwards and H. N. Wright, Am. Chem. Soc., Div. Petrol. Chem., Preprints-Symposia 1, No. 2, 63 (1956).

Synthesis of N-Methylimidazole--The synthesis of Häring (28) was to prepare N-methylimidazole. To a solution of 68 ml. of methanol and 102 ml. of 10 M sodium hydroxide, 68 g. (1.0 mole) of imidazole was added. Over a period of four hours 150 g. (1.01 mole) or 65 ml. of methyl iodide was added to the solution. The rate of addition was adjusted to keep the temperature below 35° (approximately one drop every 15 sec.). The solution was allowed to stand six hours then the methanol was removed at reduced pressure on a water bath. The residue was taken up in 200 ml. of chloroform leaving behind a large quantity of sodium iodide. The chloroform solution was dried over anhydrous sodium sulfate in the cold and distilled on Column No. 2 under vacuum. The product distilled at 89-90°C. and 17-19 mm. The yield was 37 per cent.

Instrumentation

Gas-Liquid Chromatography Instruments--A Perkin-Elmer Vapor Fractometer, Model 154-D, was used. The instrument was a standard unit using packed columns. Helium was used as the carrier gas. The recommended operating procedures were followed.

Gas-Liquid Chromatography Columns--All columns used were Perkin-Elmer commercial products. The two packed columns used were made of one-fourth inch stainless steel tubing two meters in length. The word "packed" will be omitted in further references to the packed columns. The columns used were Column A, Perkin-Elmer part number A154-1013, having a liquid phase of diisodecylphthalate and Column K, Perkin-

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28. M. Häring, Helv. Chim. Acta, 42, 1845 (1959).

Elmer part number K154-1013, having a liquid phase of polyethylene glycol.

Distillation Columns--Four distillation columns were used. Column No. 1 was a commercial Todd Column with a tantalum spiral and a vacuum takeoff head. Column No. 2 was a Todd Column with a 2 cm. diameter body packed with glass helices. Column No. 3 was a 25 cm. double-jacketed column with a 2 cm. body filled with glass helices. Column No. 4 was a Kontes Glass Company commercial distilling apparatus No. K-28710.

Table 1. Boiling Points of Some Chemicals Used

Compound	Observed Value	Literature Value
o-Chlorophenol	171-172°	176° (29)
m-Chlorophenol	212°	217° (29)
o-Cresol	187-188°	191° (30)
p-Cresol	192-193°	202° (30)
β-Dimethylaminoethanol	131-132°	134° (31)
Isobutyraldehyde	63.5-64°	63.5° (32)
Isobutyraldehyde-2-d	63.5-64°	63.5° (32)
Isobutyraldol	72-75° (3-5 mm.)	69-70° (26) (2 mm.)
2,4-Lutidine	154°	158.4° (33)

Table 1. Boiling Points of Some Chemicals Used (Continued)

Compound	Observed Value	Literature Value
3,4-Lutidine	175°	179.1° (33)

29. C. M. Judson and M. Kilpatrick, J. Am. Chem. Soc., 71, 3110 (1949).

30. R. R. Dreisbach and S. A. Shrader, Ind. Eng. Chem., 41, 2879 (1949).

31. R. D. Cadle, B. J. Robson and R. W. Moshier, J. Am. Chem. Soc., 71, 2928 (1949).

32. D. I. Coomber and J. R. Partington, J. Chem. Soc., 1938, 1444.

33. E. A. Coulson, J. D. Cox, E. F. G. Herington and J. F. Martin, J. Chem. Soc., 1959, 1934.

Table 2. Boiling Points of Some Chemicals Used

Compound	Observed Value	Literature Value
2,6-Diisopropyl-5, 5-dimethyl-4-m-dioxanol	100° (3-5 mm.)	110-111° (26) (8 mm.)
N-Methylimidazole	91° (17-18 mm.)	88° (28) (16.5 mm.)
N-Methylmorpholine	112°	116° (34)
N-Methylpiperidine	105°	103-104° (35)
N-Methylpyrrolidine	79°	78-79° (35)

Table 2. Boiling Points of Some Chemicals Used (Continued)

Compound	Observed Value	Literature Value
Phenol	173°	182-182.5° (29)
4-Picoline	143°	145° (36)
N,N,N',N'-Petramethyl-ethylenediamine	119°	119.5° (37)

34. D. D. Reynolds and W. O. Kenyon, J. Am. Chem. Soc., 72, 1597 (1950).

35. S. Searles, M. Tamres, F. Block and L. A. Quarterman, J. Am. Chem. Soc., 78, 4917 (1956).

36. D. P. Biddiscombe, E. A. Coulson, R. Handley and E. F. G. Herington, J. Chem. Soc., 1954, 1957.

37. L. Spialter and R. W. Boshier, J. Am. Chem. Soc., 79, 5955 (1957).

Table 3. Melting Points of Some Chemicals Used

Compound	Observed Value	Literature Value
p-Chlorophenol	43°	43.2-43.7° (29)
m-Nitrophenol	98-99°	96.6-96.8° (29)
p-Nitrophenol	113-114°	113.1-113.8° (29)

Table 3. Melting Points of Some Chemicals Used (Continued)

Compound	Observed Value	Literature Value
Paraisobutyraldehyde	59°	61-62° (38)

38. R. Dworzak and J. Pierri, Monatsh., 52, 145 (1929).

Ultraviolet Measurements--All the ultraviolet spectra were made with a Cary Recording Spectrophotometer, Model 14. The instrument was operated as described in the operating manual. All the spectra were made using distilled water as the solvent. A matched set of Beckman No. 46007 quartz one centimeter cells was used for all measurements. Distilled water was used in the reference cell in all cases.

Nuclear Magnetic Resonance Measurements--The nuclear magnetic resonance spectra were obtained from a Varian Nuclear Magnetic Resonance Spectrometer, Model A-60, equipped with a variable temperature probe. In order to obtain a reasonable signal to noise ratio with the dilute solutions used the r. f. frequency was set at 0.06 to 0.10 units, the filter band width at 0.20 c.p.s. and the sweep time was 250 sec. When using aqueous solutions in kinetics, the instrument was zeroed with an external standard sample of tetramethylsilane in chloroform unless otherwise indicated. The chemical shifts in water were determined using an internal standard of 3-(trimethylsilyl)-1-propanesulfonate.

Constant Temperature Baths--A constant-temperature water bath with two stirrers was used for all extended studies at 35°. The bath was a commercial instrument, American Instrument Company No. T52-428, made of insulated stainless steel and thermostated with a H-B Instrument Company thermostat No. 7536. No variation in temperature of the bath was noticeable on a thermometer graduated in tenths of a degree. The bath temperature was adjusted to 35.0 ± 0.2° using a -10 to 100° thermometer with 0.5° divisions certified by the National Bureau of Standards.

A Sargent constant-temperature water bath was used for the 60.0° studies. No variation in the temperature of the bath was noticeable on a thermometer graduated in tenths of a degree. The temperature was adjusted to 60.0 ± 0.2° using the National Bureau of Standards certified thermometer.

The short term studies--one to five hours--were made using a one gallon Dewar flask with a cover. The temperature was checked every 30 minutes and heat was supplied by adding small amounts of hot water. The temperature was maintained at 35.0 ± 0.30°. Some very short term studies were made without removing the n.m.r. sample tube from the probe of the spectrometer. As described by the Varian Corportion the magnet around the probe was maintained at a constant temperature. The temperature was 35.0 to 36.0°. The temperature was checked periodically by using a special slender thermometer prepared by the Brooklyn Thermometer Company. The thermometer was placed in a n.m.r. sample tube half filled with water and allowed to spin as would be the case during a kinetics study. The temperature did not vary more than two tenths of a degree during a given

period of time.

Melting Point and Boiling Point Determinations--Melting points were determined in capillary tubes in a circulating oil bath. Boiling points were taken as the distillation temperature of the fraction collected. All boiling points and melting points reported herein are uncorrected.

pH Measurements--A Beckman 101900 Research pH meter (115 v.) was used. The instrument was a standard unit. The readout is graduated in increments of 0.002 pH units. The instrument has a relative accuracy of $\pm$ 0.0037 pH units. Operation of the instrument was according to standard procedures. The pH scale was calibrated at a pH of 6.86 using Beckman part 22332 buffer at 25°. The measurements were made on solutions stirred with a magnetic stirrer.

Quantitative Nuclear Magnetic Resonance Spectrometry

The method used to calculate the per cent exchange in isobutyraldehyde-2-d solutions in water depended on the differences in the nuclear magnetic resonance spectra of the six hydrogens on the two alpha methyl groups of isobutyraldehyde and isobutyraldehyde-2-d in aqueous solutions. The methyl hydrogens of isobutyraldehyde-2-d are split by the alpha deuteron into a triplet centered at 8.90τ (J = 1.0 c.p.s.). The methyl hydrogens of the isobutyraldehyde are split by the alpha proton into a doublet centered at 8.91τ (J = 6.64 c.p.s.). The spectrum of a mixture of the deuterium and the protium compounds consists of five peaks corresponding to the peaks mentioned for each species in the region from 100 c.p.s. to 50 c.p.s. By examining a section of spectra from approx-

imately 100 c.p.s. to 50 c.p.s. all the peaks are observed and enough of the baseline is observed to measure the peak heights. The peak heights were measured with a transparent ruler graduated to 0.10 cm. In order to reduce the measurement error the amplitude of the instrument was increased as much as possible without causing the tallest of the five peaks to run off of the chart paper.

Isobutyraldehyde-2-d was allowed to exchange in water in the kinetic studies. An isobutyraldehyde-2-d solution, usually, 1 per cent by volume, was prepared and placed in a nuclear magnetic resonance sample tube (n.m.r. sample tube) with the catalyst to be studied. As the exchange proceeded the triplet due to the isobutyraldehyde-2-d dropped and the doublet due to the isobutyraldehyde rose. To determine the per cent exchange a series of synthetic mixtures of isobutyraldehyde-2-d and isobutyraldehyde was prepared and a standard curve was prepared by plotting a function of the peak heights versus the per cent isobutyraldehyde-2-d in the known mixtures. The function of the peak heights chosen was the height of the center peak in the isobutyraldehyde-2-d triplet, D_2, divided by the sum of the height of the D_2 peak and height of the 68 c.p.s. peak in the isobutyraldehyde doublet, H_1.

This particular function was chosen to remove some of the error that occurs due to the instability of the instrument. If the change in one peak height due to instrument instability can be assumed to be reflected by an equal degree of change in the height of the other peak, then it can be readily seen that the error due to this change in peak heights cancels out in the function of the peak heights described. This, of course, is only true if the instrument is stable during the

ten second interval necessary to make the spectrum. The plot $D_2/D_2 + H_1$ versus the per cent isobutyraldehyde-2-d is a straight line. The degree of deuteration of the isobutyraldehyde was not the same in every synthesis, but the standard curve should always have the same slope and can be used in any case (39). Table 23 contains the values obtained from the synthetic mixtures used to prepare the standard curve. To test the validity of the assumption concerning the stability of the instrument, seven independent measurements were made on a mixture of isobutyraldehyde-2-d and isobutyraldehyde and the calculated values of the extent of deuteration were all within $\pm$ 0.50 per cent of each other.

In general all of the studies were made in dilute solutions of isobutyraldehyde. In obtaining the peak heights desired the noise level became very high. The techniques used to aid in overcoming this problem were described in the section on nuclear magnetic resonance measurements. This combination of adjustments on the instrument tends to smooth out the spectra more than in the ordinary high resolution settings, but does not detract from the accuracy of the measurements. Unless otherwise indicated all the kinetic measurements were made using the techniques described here for determination of the per cent of isobutyraldehyde-2-d in a given exchanging mixture.

Aldolization Equilibrium Constant Determination

In order to obtain the equilibrium constant for the reaction

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39. J. Hine, N. W. Burske, M. Hine, and P. B. Langford, J. Am. Chem. Soc., 79, 1406 (1957).

$$2\ IBA \rightleftarrows (IBA)_2$$

it was desirable to obtain a saturated solution of the aldolization equilibrium mixture in water. A 0.293 M isobutyraldehyde solution that was 0.0097 M in sodium hydroxide was prepared by adding three ml. of 0.197 M sodium hydroxicle to 50 ml. of 0.311 M isobutyraldehyde that was 0.0026 M in isobutyric acid. The solution began to cloud and form a separate layer after approximately 30 min. The nuclear magnetic resonance spectrum indicated that the organic layer was largely 2,6-diisopropyl-5,5-dimethyl-4-m-dioxanol which is very insoluble in water. Since isobutyraldol is a precursor to the dioxanol, the organic layer must contain at least the equilibrium concentrations of isobutyraldehyde and isobutyraldol. At equilibrium the aqueous phase must contain the same three components at the same thermodynamic activities. This solution was allowed to stand for approximately one hour at room temperature, 25 $\pm$ 2°. During this time the solution became cloudy. A 10 ml. aliquot was removed and neutralized with 0.070 ml. of 1.89 M acetic acid. The resultant solution was centrifuged for five minutes and it separated into a thin layer of organic material floating on top and a lower clear aqueous phase. The nuclear magnetic resonance spectra indicated no trimer in the aqueous phase. A sample of the presumably saturated aqueous phase was diluted with an equal volume of water and the nuclear magnetic resonance and ultraviolet spectra obtained. The absorbance at the 285 mμ peak was 1.440. From nuclear magnetic resonance spectra the ratio of the concentrations of isobutyraldehyde to that of isobutyraldol can be

determined from the area of the 68.1 c.p.s. peak of isobutyraldehyde and the 63.1 c.p.s. peak of isobutyraldol.

The area of each peak can be approximated by the product of the width at half height and the height. For the isobutyraldehyde 68.1 c.p.s. signal the half width is 1.00 cm. and the height is 19.45 cm. For the isobutyraldol 63.1 c.p.s. peak the width at half height is 0.75 cm. and the height of the peak is 3.9 cm. Synthetically prepared mixtures of isobutyraldehyde and isobutyraldol had the same spectral peaks as the reaction mixture.

Actual and Apparent Extinction Coefficients of Isobutyraldol and Isobutyraldehyde

The apparent and actual extinction coefficients for isobutyraldehyde at 285 mμ were obtained by preparing an 0.1179 M isobutyraldehyde solution in water and examining the ultraviolet spectra at 285 mμ. The absorbance at 285 mμ for this solution was 1.465 the apparent extinction coefficient is, then, 12.43 but from an analysis of the nuclear magnetic resonance spectrum of aqueous isobutyraldehyde it is known that part of the isobutyraldehyde is hydrate, which will not absorb in the ultraviolet at 285 mμ. The equilibrium constant for the hydration of isobutyraldehyde at 25° C. is 0.604. The concentration of free isobutyraldehyde (x) may therefore be calculated from the following equation

$$K = \frac{IBAOH_2}{IBA} = \frac{(0.1179 - x)}{x}$$

The value obtained is 0.0819 M and the actual extinction coefficient is

19.93.

The nuclear magnetic resonance spectrum of aqueous isobutyraldol does not indicate the presence of a hydrate. The extinction coefficient of isobutyraldol at its 285 mμ maximum was obtained from the examination of 0.07806 M and 0.03903 M isobutyraldol solutions in one centimeter cells.

Table 4. Isobutyraldol Extinction Coefficient

Concentration	Adsorbance	ε
0.07803	1.930	24.72
0.03903	0.970	24.85
		Average 24.78

Acidity of Isobutyraldehyde Hydrate

When isobutyraldehyde is in aqueous solution a new doublet appears shifted 11.5 cps upfield from the doublet due to the methyl hydrogens of the aldehyde. This doublet is due to the hydrate. In order to learn the extent to which this hydrate might neutralize basic catalysts, it was necessary to determine its acid dissociation constant.

The acidity of isobutyraldehyde hydrate was determined by examining the ultraviolet spectrum of an aqueous isobutyraldehyde solution containing hydroxide ion. Isobutyraldehyde has an ultraviolet spectrum with a peak at 285 mμ with an apparent extinction coefficient of 12.43. A 0.236

M solution of isobutyraldehyde prepared under nitrogen was used for these studies. The solution was 0.0046 M in isobutyric acid. To determine the optical density of the 0.236 M isobutyraldehyde solution, one ml. of the solution and one ml. of distilled water was placed into a one centimeter cell and the spectrum examined.

To determine the amount of isobutyraldehyde that had been converted to the anion of the hydrate, a matched one centimeter cell was flushed with nitrogen and one ml. of 0.2358 M isobutyraldehyde solution and 1.0 ml. of the 0.1974 M sodium hydroxide solution injected into the cells and shaken vigorously. The optical density of the 285 mμ peak of isobutyraldehyde was determined. The absorbance in a one centimeter cell of the solution of 0.1179 M isobutyraldehyde and 0.0987 M sodium hydroxide was 1.385 and the absorbance of the 0.1179 M isobutyraldehyde was 1.465 The results of this study are discussed in the section on the acidity of the hydrate in Chapter III.

Hydroxide Ion Catalyzed Rate of Deuterium Exchange

To determine the specific rate constant for the hydroxide ion catalyzed exchange of isobutyraldehyde, the quenching technique as described in the general kinetics section was used.

Experiment No. 1. To 10 ml. of 2 per cent isobutyraldehyde-2-d prepared by injecting 0.20 ml. of isobutyraldehyde-2-d into 9.80 ml. of distilled water covered with nitrogen was added to 0.15 ml. of 0.973 M sodium hydroxide at zero time. The water had been thermally equilibrated previously in a 35° C. constant-temperature bath. The reaction vessel was a 25 ml. ground glass flask. Every time a sample was removed the

top of the flask was swept with nitrogen. The results of this experiment are in Table 24.

Experiment No. 2. This experiment run exactly as Experiment No. 1 except 0.20 ml. of 0.973 M sodium hydroxide was used. The results are in Table 25.

Experiment No. 3. An attempt was made to follow the exchange without quenching the base. One milliliter of 2 per cent isobutyraldehyde-2-d solution was injected into a nitrogen-filled n.m.r. sample tube. At zero time 0.035 ml. of 0.973 M sodium hydroxide was injected into the n.m.r. sample tube. The spectrum was blurred but rough data were obtained. A sample of the 2 per cent isobutyraldehyde-2-d solution was titrated with sodium hydroxide as it was impossible to remove the exchange mixture from the n.m.r. sample tube easily. The results are recorded in Table 26.

Hydrogen Ion Catalyzed Exchange of Isobutyraldehyde-2-d

In order to determine the rate constant for the hydrogen ion catalyzed exchange of isobutyraldehyde-2-d, 0.50 ml. of 1.696 M perchloric acid was added to one milliliter of isobutyraldehyde-2-d solution in a nitrogen-filled n.m.r. sample tube. The kinetics were studied by examining the nuclear magnetic resonance spectrum of the solution from time to time.

In acid concentrations of the strength used in this study the peaks due to the isobutyraldehyde and the hydrate are fused; because of the rapid chemical exchange the instrument cannot determine which environment the proton is a part of at any time. Instead of having a doublet

at 8.91τ for the isobutyraldehyde and another doublet at 9.07τ for the hydrate there is only one doublet at 8.97τ with J = 6.9 c.p.s. In the case of the isobutyraldehyde-2-d there is only one triplet at 8.98τ with J = 1.00 c.p.s. To obtain the peak heights due to the aldehyde the fused peak height would have to be multiplied by the per cent free aldehyde in an aqueous solution but in the kinetic plot this term will cancel out. The results are in Table 27.

Kinetics of Dealdolization of Isobutyraldol

Two different techniques were used to determine the hydroxide-catalyzed rate of dealdolization of isobutyraldol. A solution of isobutyraldol was prepared by weighing isobutyraldol into a volumetric flask and diluting with distilled water. At zero time, 0.08 ml. of 0.0197 M sodium hydroxide was added to 0.90 ml. of 0.0636 M isobutyraldol. The isobutyraldol solution was titrated before the study was made and found to be 0.0013 M in acid. Plots of the kinetics gave curved lines and at the end of the study a sample of the exchange solution turned yellow on addition of a drop of bromothymol blue. Slight oxidation of the aldehyde would neutralize the base and explain the difficulty.

In order to obtain a constant hydroxide ion concentration in spite of the slight oxidation, a buffer of triethylenediamine was used. Westheimer and Cohen (2) found that tertiary amines do not catalyze the dealdolization of diacetone alcohol. In Experiment 1, 0.25 ml. of a buffer of 0.120 M triethylenediamine and 0.0194 M triethylenediamine monohydroperchlorate was added to 0.50 ml. of 0.0636 M isobutyraldol. The

aldol solution was 0.0013 M in acid. In Experiment 2, 0.25 ml. of a buffer of 0.0716 M triethylenediamine and 0.0445 M triethylenediamine monohydroperchlorate was added to 0.50 ml. of 0.0794 M isobutyraldol. The aldol solution was 0.00158 M in acid. The solutions were added together in a nitrogen-filled n.m.r. sample tube and shaken. The kinetics gave linear plots for the buffered dealdolization. Table 5 is a tabulation of the three buffers used and concentrations of the various components. Figure 1 is a kinetic plot of Experiment No. 2.

Table 5. Concentrations Used in Dealdolization Kinetic Studies

Component	Concentrations in Moles per Liter Experiment Number		
	1	2	3
Triethylenediamine	0.039	0.0228	
Triethylenediamine Monohydroperchlorate	0.0074	0.0159	
Trimethylamine			0.0086
Trimethylammonium Perchlorate			0.0070
Acid	0.00088	0.00104	0.00104
Table No.	28	29	30

The results are tabulated in Tables 28, 29 and 30.

One study (Experiment No. 3) was made using a different buffer 0.0278 M trimethylamine--0.0180 M trimethylammonium perchlorate. In a nitrogen-filled m.n.r. tube 0.50 ml. of 0.0794 M isobutyraldol was injected into 0.25 ml. of the trimethylamine--trimethylammonium perchlorate

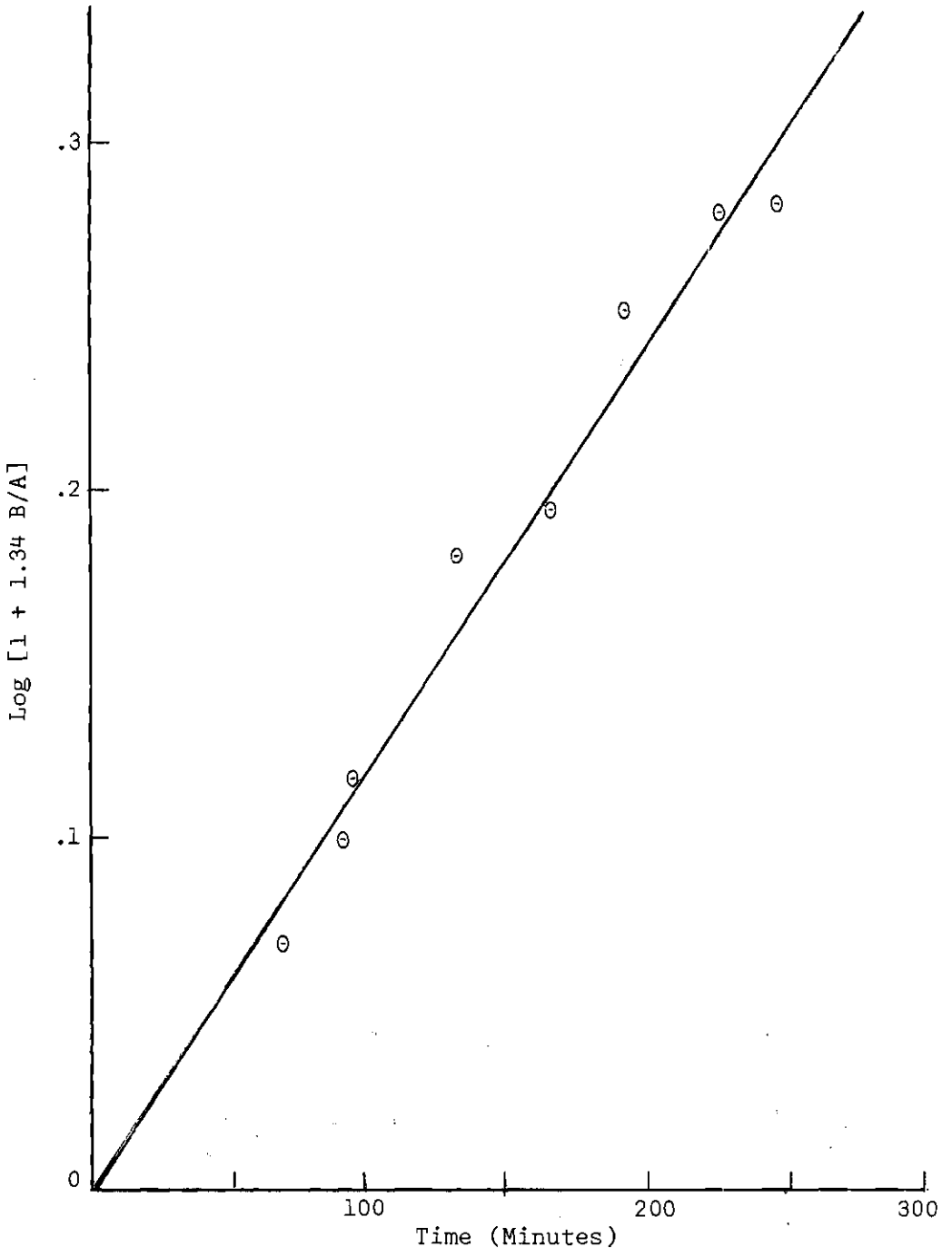

Figure 1. Kinetic Plot of the Dealdolization of Isobutyraldol by 0.0229 M Triethylenediamine--0.0158 M Triethylenediamine Monohydroperchlorate

buffer. The isobutyraldol solution was 1.58×10^{-3} M in acid.

Acidity of the Isobutyraldehyde Solutions

To determine the amount of oxidation of the isobutyraldehyde during the handling, it was necessary to titrate samples of the isobutyraldehyde solution that was used quite frequently. It was necessary to use a technique that was rapid. The indicator used was bromothymol blue, which has an indicator range of pH 6.0 to 7.6 (40). Isobutyric acid has an ionization constant of 1.76×10^{-5} at 25° C. (41).

The technique used was to remove 0.50 ml. samples of the prepared isobutyraldehyde solutions at various times during a kinetics study and inject the sample into a capped two milliliter vial containing 0.50 ml. distilled water and three drops of bromothymol blue indicator. The cap had several small holes just large enough to allow a needle to be inserted through in it. To titrate, a 1.00 ml. syringe was filled with sodium hydroxide solution and used to measure the base added. The end point was considered to be the green color between the yellow acid color and the deep blue base color of the indicator. The titrations were always made in duplicate.

Kinetic Studies

The kinetic experiments were conducted using one of three tech-

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40. J. F. Masi and S. B. Knight, J. Am. Chem. Soc., 67, 1558 (1945).

41. D. H. Everett, D. A. Landsman and B. R. Pinsert, Proc. Roy. Soc. (London), A215, 403 (1952).

niques. Each of these techniques was required to overcome a specific problem.

Quenching Technique

Under exchange conditions in which the hydroxyl ion concentration exceeded 0.003 M the rate of hydration and dehydration of isobutyraldehyde was so rapid that the instrument can only show an average of the peaks of the hydrate and isobutyraldehyde. In the intermediate cases (0.0001 to 0.003 M) the peaks blur into a jumbled mess.

In cases like this it is necessary to neutralize the base with a weak acid that does not catalyze the exchange efficiently. Experiments indicated that acetate ion and acetic acid are poor exchange catalysts. Generally the procedure then consisted of preparing 10 ml. of a 0.2 M isobutyraldehyde-2-d solution in water. To do this 9.8 ml. of water and 0.20 ml. of isobutyraldehyde-2-d were added and allowed to equilibrate in the 35° constant-temperature bath. An inverted funnel was placed so nitrogen could sweep over the top of the flask on opening. To this mixture at zero time the catalyst was added, usually less than 0.50 ml. At regular intervals, usually 10 min., a 0.50 ml. sample of the exchange mixture was removed with a 1.00 ml. syringe. This sample was rapidly injected into an n.m.r. sample tube containing at least 10 per cent more than enough concentrated acetic acid (0.05 ml.) to neutralize the base. These samples could stand for several hours without noticeable changes in the per cent of isobutyraldehyde-2-d. The per cent isobutyraldehyde-2-d was then determined as previously described. At various times during the study, usually at the beginning, in the middle, and at the end of the experiment, 0.50 ml. samples of the exchange mixture were removed and

titrated to determine the degree of oxidation.

General Technique

For weaker bases the spectrum of isobutyraldehyde-2-d was very clear without neutralizing the base. An n.m.r. sample tube was flushed with nitrogen and then 0.50 ml. of 0.20 M isobutyraldehyde was injected into the n.m.r. sample tube. Several of the isobutyraldehyde-2-d filled tubes were allowed to equilibrate in the one gallon Dewar flask in the Nuclear Magnetic Resonance Instrument room. At zero time 0.25 ml. of the catalyst, usually as a buffer, was injected into the isobutyraldehyde-2-d solution and shaken vigorously for a minute. At various times the n.m.r. sample tubes were removed from the Dewar flask and placed in the nuclear magnetic resonance probe to determine the per cent isobutyraldehyde-2-d at that time. In this way several different catalysts could be studied at one time. If the exchange was very rapid the n.m.r. sample tube could remain in the probe until completion of reaction since the temperature of the probe was that of the constant-temperature bath.

Slow Reaction Technique

In some cases the exchange was very slow and the solubility of the catalyst low. To obtain the most concentrated exchange mixture the following procedure was used. An almost saturated solution of catalyst was prepared and 1.00 ml. was syringed into the nitrogen-filled n.m.r. sample tube. To this 0.05 ml. of pure isobutyraldehyde-2-d was added and the mixture shaken. The aldehyde concentration is about the same as before, but the catalyst is not diluted very much. The amount of isobutyric acid in the isobutyraldehyde-2-d was determined by preparing

a 0.3 M isobutyraldehyde-2-d solution and titrating a 1.00 ml. sample with sodium hydroxide.

All the buffers used in the following studies were prepared by weighing the amine or phenol into a volumetric flask filled with nitrogen and then pipetting the acid or base into the flask. The mixture was then diluted to the mark of the volumetric flask. In cases where heat was evolved the mixture was allowed to cool before adding the water. Unless otherwise indicated the kinetics were studied using the general technique indicated previously. All the studies were done at 35° ± 0.2°.

Triethylamine Catalysis. Using the quenching technique, kinetics of the exchange of isobutyraldehyde-2-d with triethylamine--triethylammonium perchlorate buffer was studied. In a 25 ml. glass-stoppered flask at zero time 5.0 ml. of isobutyraldehyde-2-d solution and 2.50 ml. of a buffer composed of 0.0563 M triethylamine and 0.106 M triethylammonium perchlorate were mixed. The aldehyde solution was 0.0078 M in isobutyric acid. Also 0.025 ml. of tert-butyl alcohol was added. The final solution was 0.0136 M in triethylamine and 0.040 M in triethylammonium ion.

The t-butyl alcohol was added as an internal reference at 73.5 c.p.s. in water. The methyl hydrogens in triethylammonium ion are included in the 68 c.p.s. peak due to isobutyraldehyde. During the reaction the ratio of the areas of the t-butyl alcohol peak and the triethylammonium ion peak should remain constant. By determining the ratio at zero time before the portion of the 68 c.p.s. peak due to the isobutyraldehyde appears, it is possible to calculate the contribution of

the triethylammonium ion to the 68 c.p.s. peak at any time during the study, by knowing the height of the reference peak, t-butyl alcohol. When the triethylammonium ion contribution is subtracted from the total peak, the remainder is the isobutyraldehyde 68 c.p.s. peak and the kinetics calculations can be made as usual. The results are in Table 31.

Trimethylamine Catalysis. The kinetics of the trimethylamine catalyzed exchange were complicated in the more concentrated solutions by the rapid formation of an insoluble material assumed to be an aldol condensation product. As a consequence several experiments were made. These studies were made using sodium perchlorate to maintain the ionic strength constant.

Experiment No. 1--To 1.00 ml. of isobutyraldehyde-2-d solution in a nitrogen-filled n.m.r. sample tube was added 0.040 ml. of a buffer containing 0.973 M trimethylamine and 0.857 M trimethylammonium perchlorate. The isobutyric acid concentration of the isobutyraldehyde-2-d solution was 0.0064 M. The final concentration of the trimethylamine was 0.0312 M and that of the trimethylammonium ion 0.0392 M.

Experiment No. 2--To 1.00 ml. of isobutyraldehyde-2-d solution in a nitrogen-filled n.m.r. sample tube was added 0.020 ml. of a buffer composed 0.973 M trimethylamine and 0.857 M trimethylammonium perchlorate. The isobutyric acid concentration of the isobutyraldehyde solution was 0.0064 M. To maintain the ionic strength as in Experiment No. 1, 0.020 ml. of 0.853 M sodium perchlorate was added. The final concentration of the solution was 0.0125 M trimethylamine and 0.0227 M trimethylammonium ion.

Experiment No. 3--Into 1.00 ml. of isobutyraldehyde-2-d solution in a nitrogen-filled n.m.r. sample tube was injected 0.030 ml. of a buffer of 0.973 M trimethylamine and 0.857 M trimethylammonium perchlorate. Also 0.010 ml. of 0.853 M sodium perchlorate was added. The isobutyraldehyde-2-d solution contained 0.0064 M isobutyric acid. The final concentration of the trimethylamine was 0.0218 M and the trimethylammonium ion was 0.0309 M.

Experiment No. 4--This experiment was done at a somewhat later time to check the previous results. The buffer was titrated and apparently a large part of the free amine had evaporated. To study the kinetics, 0.25 ml. of a buffer containing 0.0691 M trimethylamine and 0.036 M trimethylammonium ion and 0.003 M sodium perchlorate was added to 0.50 ml. of isobutyraldehyde-2-d solution containing 0.0225 M isobutyric acid. The final concentration of trimethylamine was 0.0080 M and the trimethylammonium ion was 0.027 M. The results are in Tables 32, 33, 34, 35.

N-Methylmorpholine. Using the kinetic technique described for weak bases, the kinetics of the N-methylmorpholine-catalyzed exchange was studied. Into 0.25 ml. of a buffer composed of 0.120 M N-methylmorpholine and 0.0663 M N-methylmorpholinium perchlorate was injected 0.50 ml. of isobutyraldehyde-2-d solution that was 0.0231 M in isobutyric acid. The final concentration of N-methylmorpholine was 0.0246 M and that of N-methylmorpholinium ion was 0.0375 M. The results are included in Fig. 3 and Table 36.

1,4-Diazabicyclo [2.2.2]octane. To study 1,4-diazabicyclo[2.2.2]-octane, 0.25 ml. of a buffer composed of 0.120 M 1,4-diazabicyclo[2.2.2]-

octane (triethylenediamine) and 0.0194 M 1,4-diazabicyclo[2.2.2]octane hydrogen perchlorate was added to 0.50 ml. of isobutyraldehyde-2-d solution containing 0.0225 M isobutyric acid. The final concentration of 1,4-diazabicyclo[2.2.2]octane was 0.0250 M and the concentration of 1,4-diazabicyclo[2.2.2]octane hydrogen perchlorate was 0.0215 M. The results are tabulated in Table 37 and Fig. 3.

1,4-Diazabicyclo[2.2.2]octane Hydrogen Perchlorate. An attempt was made to study the catalysis by a 0.0274 M solution of 1,4-diazabicyclo[2.2.2]octane hydrogen perchlorate. After one week there was no indication of exchange and the experiment was abandoned.

β-Dimethylaminoethanol. The study of the β-dimethylaminoethanol catalyzed exchange of isobutyraldehyde-2-d was accomplished by adding 0.25 ml. of a buffer consisting of 0.100 M β-dimethylaminoethanol and 0.0895 M β-dimethylaminoethanol hydrogen perchlorate to 0.50 ml. of an isobutyraldehyde-2-d solution. The isobutyraldehyde-2-d solution contained 0.0077 M isobutyric acid. The final concentration of β-dimethylaminoethanol was 0.0281 M and that of the β-dimethylaminoethanol hydrogen perchlorate was 0.0350 M. The results are included in Table 38 and Fig. 3.

N-Methyldiethylamine. The study of the kinetics of the isobutyraldehyde-2-d exchange catalyzed by N-methyldiethylamine was accomplished by injecting 0.25 ml. of a buffer consisting of 0.0876 M N-methyldiethylamine and 0.135 M N-methyldiethylammonium perchlorate in 0.50 ml. of isobutyraldehyde-2-d solution. The aldehyde solution was 0.0158 M in isobutyric acid. The final solution consisted of 0.0187 M N-methyldiethylamine and 0.0556 M N-methyldiethylammonium ion. The results are

included in Fig. 3 and are tabulated in Table 39.

N,N,N',N'-Tetramethylethylenediamine. The study of the kinetics of the N,N,N',N'-tetramethylethylenediamine-catalyzed exchange of isobutyraldehyde was made by injecting 0.25 ml. of a buffer, 0.1283 M in N,N,N',N'-tetramethylethylenediamine and 0.1352 M in the monoammonium perchlorate, into 0.50 ml. of isobutyraldehyde-2-d solution that contained 0.0158 M isobutyric acid. The final concentration of the N,N,N',N'-tetramethylethylenediamine was 0.0323 M and the concentration of the monoammonium solution was 0.0556 M. The results are tabulated in Table 40 and Fig. 3.

N-Methylimidazole. The study of the N-methylimidazole-catalyzed exchange of isobutyraldehyde-2-d was made by injecting 0.05 ml. of isobutyraldehyde-2-d into one ml. of a buffer of 0.1727 M N-methylimidazole and 0.3380 M N-methylimidazole hydrogen perchlorate. From the titration of a standard isobutyraldehyde solution prepared at the time, the isobutyraldehyde-2-d contained 0.405 M isobutyric acid. The final concentration of the N-methylimidazole was 0.1454 M and that of the hydrogen perchlorate was 0.3408 M.

A second N-methylimidazole study was made using the same buffer--0.1727 M N-methylimidazole and 0.3380 M N-methylimidazole hydrogen perchlorate. To an n.m.r. sample tube containing 0.50 ml. of isobutyraldehyde-2-d was injected 0.25 ml. of buffer. The isobutyraldehyde-2-d solution contained 0.0158 M isobutyric acid. The final concentration of N-methylimidazole was 0.0471 M and that of the N-methylimidazole hydrogen perchlorate was 0.1232 M. The results are recorded in Tables 41 and 42.

2,2',2''-Nitrilotriethanol. The study of the kinetics of the 2,2',2''-nitrilotriethanol (triethanolamine) catalyzed exchange of isobutyraldehyde-2-d was made by injecting 0.05 ml. of isobutyraldehyde-2-d into 1.0 ml. of a buffer composed of 0.257 M 2,2',2''-nitrilotriethanol and 0.141 M 2,2',2''-nitrilotriethanol hydrogen perchlorate. The isobutyraldehyde-2-d contained 0.1743 M isobutyric acid. The final concentration of the 2,2',2''-nitrilotriethanol was 0.237 M and that of the hydrogen perchlorate was 0.142 M. The results are tabulated in Table 43 and Figure 3.

Acetate Ion Catalysis. The acetate ion catalyzed exchange was studied at two buffer ratios to learn whether the exchange was catalyzed by the acetic acid. The studies were carried out over an extended period of time; therefore the capped n.m.r. sample tubes were sealed as tightly as possible.

Experiment No. 1--To 0.50 ml. of isobutyraldehyde-2-d solution was added 0.50 ml. of a buffer composed of 0.6385 M acetic acid and 0.6385 M acetate ion. The final concentration of acetic acid was 0.319 M and that of the acetate ion was 0.319 M.

Experiment No. 2--To one ml. of a buffer composed of 0.164 M acetic acid and 0.875 M acetate ion was added 0.05 ml. of isobutyraldehyde-2-d. The final concentration of the buffer was 0.1561 M acetic acid and 0.833 M acetate ion. The results of these experiments are tabulated in Tables 44 and 45 and Fig. 3.

2,4-Lutidine. The kinetics of the exchange of isobutyraldehyde-2-d using 2,4-lutidine as a catalyst were studied by injecting 0.25 ml. of 0.526 M 2,4-lutidine into 0.50 ml. of isobutyraldehyde-2-d solution. The aldehyde solution was 0.0078 M in isobutyric acid. The concentra-

tion of 2,4-lutidine was 0.170 M and the 2,4-lutidinium ion was 0.005 M. The results are included in Fig. 3 and Table 46.

4-Picoline. To study the 4-picoline-catalyzed exchange of isobutyraldehyde-2-d, 0.25 ml. of buffer composed of 0.1983 M 4-picoline and 0.3380 M 4-picolinium perchlorate was added to a n.m.r. sample tube containing 0.50 ml. of isobutyraldehyde-2-d solution that was 0.0158 M in isobutyric acid. The final concentration of the buffer was 0.0556 M 4-picoline and 0.1232 M 4-picolinium ion.

The kinetics were also studied using more concentrated buffer. Into one ml. of the buffer used previously was injected 0.05 ml. of isobutyraldehyde-2-d. The concentration of isobutyric acid in the aldehyde was determined by preparing a standard solution and titrating it. The acid concentration in the isobutyraldehyde-2-d was 0.405 M. The final concentration of 4-picoline was 0.1788 M and that of 4-picolinium ion was 0.3408 M. The results of these studies are in Fig. 3 and Tables 47 and 48.

2,4,6-Trimethylpyridine. The kinetics of the 2,4,6-trimethylpyridine-catalyzed exchange of isobutyraldehyde-2-d were studied by injecting 0.05 ml. of isobutyraldehyde-2-d into one ml. of a buffer consisting of 0.1172 M 2,4,6-trimethylamine and 0.1357 M 2,4,6-trimethylpyridinium perchlorate. The acid concentration was determined as before and was 0.473 M. The final concentration of the buffer was 0.0891 M 2,4,6-trimethylpyridine and 0.1512 M 2,4,6-trimethylpyridinium ion. The results are tabulated in Table 49 and Fig. 3.

2,6-Lutidine. The 2,6-lutidine-catalyzed exchange was studied by injecting 0.05 ml. of isobutyraldehyde-2-d into one ml. of a buffer

containing 0.1920 M 2,6-lutidine and 0.338 M 2,6-lutidinium perchlorate. The concentration of isobutyric acid in the isobutyraldehyde-2-d was 0.473 M. The final concentration of the buffer was 0.161 M in 2,6-lutidine and 0.345 M in 2,6-lutidinium ion. The results are tabulated in Table 50 and Fig. 3.

Pyridine. The kinetic study of the pyridine-catalyzed exchange was made by injecting 0.05 ml. isobutyraldehyde-2-d into one ml. of a buffer composed of 0.758 M pyridine and 0.217 M pyridinium perchlorate. The isobutyric acid concentration was 0.174 M in the isobutyraldehyde-2-d. The final concentration of the buffer was 0.714 M in pyridine and 0.215 M in pyridinium ion. The results are included in Table 51 and Fig. 3.

3,4-Lutidine. The 3,4-lutidine-catalyzed exchange of isobutyraldehyde-2-d was studied by injecting 0.05 ml. of isobutyraldehyde-2-d into a buffer composed of 0.142 M 3,4-lutidine and 0.109 M 3,4-lutidinium perchlorate. The buffer was prepared at higher concentrations but white solid formed almost at once. The isobutyric acid concentration in the aldehyde was 0.174 M. The final concentration of the buffer was 0.127 M in 3,4-lutidine and 0.112 M in 3,4-lutidinium ion. The results are tabulated in Table 52 and Fig. 3.

Trimethylamine-N-Oxide. The kinetics of the trimethylamine-N-oxide-catalyzed deuterium exchange were studied by injecting 0.050 ml. of isobutyraldehyde-2-d into one ml. of a buffer composed of 0.359 M trimethylamine-N-oxide and 0.071 M trimethylamine-N-oxide hydrogen perchlorate. The isobutyric acid concentration was 0.3418 M in the isobutyraldehyde-2-d. The final concentration of the buffer was 0.332 M

trimethylamine-N-oxide and 0.078 M in trimethylamine-N-oxide hydrogen perchlorate or isobutyrate ion. The isobutyric acid concentration is 0.003 M and the isobutyrate ion is 0.0101 M. Results are in Table 53 and Fig. 3.

Phenol. The kinetics of the phenoxide catalyzed exchange of isobutyraldehyde-2-d was studied by injecting 0.25 ml. of a buffer composed of 0.0956 M phenol and 0.0956 M sodium phenoxide into 0.50 ml. of isobutyraldehyde solution. The isobutyric acid concentration of the isobutyraldehyde-2-d solution was 0.0078 M. The final concentration of the buffer was 0.0371 M phenol and 0.0267 M phenoxide ion.

The experiment was repeated using a buffer composed of 0.0659 M phenol and 0.1257 M sodium phenoxide. The isobutyric acid concentration of the isobutyraldehyde-2-d solution was 0.0179 M. The final concentration of the buffer was 0.0339 M phenol and 0.0299 M phenoxide ion. The results are in Table 54 and 55 and are included in Fig. 3.

m-Chlorophenol. The study of the kinetics of the exchange of isobutyraldehyde-2-d catalyzed by m-chlorophenoxide ion was accomplished by use of a mixture of 0.25 ml. of a buffer containing 0.0820 M m-chlorophenol and 0.1186 M sodium m-chlorophenoxide and 0.50 ml. of an isobutyraldehyde-2-d solution. The isobutyraldehyde-2-d solution contained 0.0179 M isobutyric acid. The final concentration of the buffer was 0.0393 M m-chlorophenol and 0.0275 M sodium m-chlorophenoxide ion. The results are included in Fig. 3 and Table 56.

p-Chlorophenol. The kinetics of the exchange of isobutyraldehyde-2-d in the presence of p-chlorophenoxide ion was studied by the use of a mixture consisting of 0.25 ml. of a buffer 0.1522 M p-chlorophenol--

0.1581 M sodium p-chlorophenoxide and 0.50 ml. of isobutyraldehyde-2-d solution. The isobutyraldehyde-2-d solution contained 0.0179 M isobutyric acid. The final concentration of the buffer was 0.0627 M p-chlorophenol--0.0407 M p-chlorophenoxide ion. The results are tabulated in Table 57 and included in Fig. 3.

o-Chlorophenol. The kinetics of the o-chlorophenoxide catalyzed exchange of isobutyraldehyde-2-d was studied by injecting 0.25 ml. of a buffer 0.1880 M o-chlorophenol--0.1576 M sodium o-chlorophenoxide into 0.75 ml. of isobutyraldehyde-2-d solution. The aldehyde solution contained 0.020 M isobutyric acid. The final concentration of buffer was 0.0620 M o-chlorophenol--0.0244 M sodium o-chlorophenoxide. The results are tabulated in Table 58 and included in Fig. 3.

o-Methylphenol (o-Cresol). The kinetics of the exchange of isobutyraldehyde-2-d catalyzed by o-methylphenoxide ion were studied by adding 0.25 ml. of a buffer of 0.0239 M o-methylphenol--0.1570 M sodium o-methylphenoxide to 0.75 ml. of isobutyraldehyde-2-d solution. The isobutyric acid concentration of the aldehyde solution was 0.020 M. The final concentration of the buffer was 0.0210 M o-methylphenol--0.0243 M o-methylphenoxide ion. The results are tabulated in Table 59 and included in Fig. 3.

p-Methylphenol (p-Cresol). The study of the kinetics of the exchange of isobutyraldehyde-2-d catalyzed by p-methylphenoxide ion was made by injecting 0.25 ml. of a buffer consisting of 0.1222 M p-methylphenol--0.1186 M sodium p-methylphenoxide into 0.50 ml. of isobutyraldehyde-2-d solution. The aldehyde solution contained 0.0179 M isobutyric acid. The final concentration of the buffer was 0.0527 M p-methyl-

phenol--0.0275 M p-methylphenoxide ion. The results are tabulated in Table 60 and included in Fig. 3.

m-Nitrophenol. The study of the kinetics of the exchange of isobutyraldehyde-2-d catalyzed by m-nitrophenoxide ion was carried out by injecting 0.25 ml. of a buffer composed of 0.0659 M m-nitrophenol--0.0790 M sodium m-nitrophenoxide into 0.50 ml. of isobutyraldehyde-2-d solution. The aldehyde solution was 0.0179 M isobutyric acid. The final concentration of the buffer was 0.0340 M m-nitrophenol--0.0143 M m-nitrophenoxide ion. The results are tabulated in Table 61 included in Fig. 3.

p-Nitrophenol. The kinetics of the p-nitrophenoxide catalyzed exchange of isobutyraldehyde-2-d was studied by injecting 0.50 ml. of a buffer composed of 0.0536 M p-nitrophenol--0.0790 M sodium p-nitrophenoxide into 0.50 ml. of isobutyaldehyde-2-d solution containing 0.0200 M isobutyric acid. The final concentration of the buffer was 0.0368 M p-nitrophenol--0.0295 M p-nitrophenoxide. The results are tabulated in Table 62.

N-Methylpiperidine. The kinetics of N-methylpiperidine-catalyzed exchange of isobutyraldehyde-2-d was studied using a sample of 0.50 ml. of isobutyraldehyde and 0.15 ml. of a buffer composed of 0.083 M N-methylpiperidine and 0.052 M N-methylpiperidinium perchlorate. The isobutyric acid concentration in the aldehyde solution was 0.0048 M. The final concentrations were 0.0154 M N-methylpiperidine and 0.0157 M N-methylpiperidinium perchlorate. The results are in Table 63.

N-Methylpyrrolidine. The kinetics of N-methylpyrrolidine-catalyzed exchange of isobutyraldehyde-2-d was studied using a reaction

mixture of 0.50 ml. of isobutyraldehyde-2-d solution and 0.15 ml. of a buffer composed of 0.080 M N-methylpyrrolidine and 0.105 M N-methylpyrrolidinium perchlorate. The isobutyric acid concentration of the aldehyde solution was 0.0048 M. The concentration of the reaction components were 0.0148 M N-methylpyrrolidine and 0.0279 M N-methylpyrrolidinium perchlorate. The results are tabulated in Table 64.

Rate of Deuterium Exchange at 60°

The rate of exchange of isobutyraldehyde-2-d was studied at 60° using a constant temperature bath as described in the instrument section. In order to determine the catalysis due to water but prevent catalysis by acid unavoidably present, a very dilute, ineffective catalyst was used. Into 10 ml. of 0.0050 M sodium acetate was injected 0.35 ml. of isobutyraldehyde-2-d. The sodium acetate had been purged with nitrogen and pipetted into a 15 ml. rubber-capped vial that had been flushed with nitrogen. The syringe was purged with nitrogen and the isobutyraldehyde-2-d was transferred under a cover of nitrogen. The rate of catalysis at room temperature is slow enough to be ignored compared to the rate at 60°. This solution was 0.00252 M in isobutyric acid. The isobutyraldehyde-2-d concentration was 0.278 M and the acetate ion concentration 0.00483 M. Three 1 ml. samples of this solution were injected into n.m.r. sample tubes that were flushed with nitrogen and capped. These tubes were sealed by warming the tube near the cap, inserting a needle into the cap and pulling the tube down and sealing it. The free volume left in the tubes was approximately 0.50 ml. These samples were placed in the 60° constant temperature bath and the kinetics followed by re-

moving the samples and placing them in water at 25° to essentially stop the catalysis during the analysis. The time was counted only when the samples were in the constant temperature bath. The samples were opened and titrated when the kinetics study was completed. The samples titrated 0.0049 M in acid.

Rate of Deuterium Exchange at 100° C

Using the same technique as used in the 60° C rate study, 5.0 ml. of 0.0050 M sodium acetate was pipetted into a 10 milliliter rubber-capped vial. Into this solution was injected 0.175 ml. of isobutyraldehyde-2-d. The final concentration of acetate was 0.00483 M and that of isobutyraldehyde-2-d was 0.278 M. The solution was 0.035 M in isobutyric acid. Three 1.0 ml. samples were injected into n.m.r. sample tubes and sealed as in the 60° study. The constant temperature bath was a three-neck flask, two-thirds full of refluxing water. In one neck was a reflux condenser and the other two were stoppered. Two of the sealed tubes were floated in a cork in this bath. They were removed from time to time, cooled in tap water and the nuclear magnetic resonance spectra examined. The exchange was timed only when the n.m.r. sample tubes were in the 100° bath. The third tube was allowed to sit at room temperature, 25°. No exchange was observed in this sample during the time of the study. The tubes were opened and the samples titrated when the kinetics were stopped. The samples titrated 0.0054 M in acid. The results are in Table 66.

Two Component--Acid-Base--Catalyst System

In the two component catalyst a mixture of methylammonium chloride

and a buffer of N-methylmorpholine and N-methylmorpholinium perchlorate was added to the isobutyraldehyde-2-d solution. Two separate studies were made. In one study the concentration of N-methylmorpholine buffer was held constant and the buffer ratio was maintained at a value of one, but the methylammonium chloride concentration was varied over a five-fold range from 0.044 M to 0.22 M. A plot of the observed first-order rate constants for exchange versus the concentration of the methylammonium chloride yielded a straight line.

A second study was made to determine the slope of the line obtained by plotting the observed first-order rate constant for exchange in a series of experiments in which the concentration of methylammonium chloride was held constant and the buffer concentration varied.

In these studies the ionic strength was held constant by adding sodium perchlorate. In general all the studies were done in the same way. The buffer, methylammonium chloride solution and sodium perchlorate solution were injected into a nitrogen-filled n.m.r. sample tube and then at zero time the 0.55 M isobutyraldehyde-2-d solution was syringed into the mixture, which was then shaken vigorously.

In the following group of experiments the samples used for the exchange studies were prepared by injecting the catalysts into an n.m.r. sample tube that had been previously filled with nitrogen. In the first group of experiments, 0.50 ml of a buffer composed of 0.422 M N-methylmorpholine and 0.424 M N-methylmorpholinium perchlorate was syringed into an n.m.r. sample tube. Then a total of 0.25 ml. of 0.88 M methylammonium chloride and 0.88 M sodium perchlorate was added. Table 6 gives the exact quantities used in each experiment and the final concentra-

tions. At zero time 0.25 ml. of isobutyraldehyde-2-d solution was added and the n.m.r. sample tube was shaken, capped and placed in a 35° constant temperature bath. The nuclear magnetic spectrum was examined periodically to determine the extent of exchange. The isobutyric acid concentration of the aldehyde solution was small enough to ignore.

Table 6. Constant Buffer Concentration Deuterium Exchange Experiments at Ionic Strength 0.43

0.211 M N-Methylmorpholine 0.14 M Isobutyraldehyde

0.212 M N-Methylmorpholinium Perchlorate

Experiment No. 2c	Milliliter 0.88 M $MeNH_3Cl$	Milliliter 0.88 M $NaClO_4$	Final Concentration $MeNH_3Cl$	Table Number
16, 26, 32	0.25	0	0.220	67
17	0	0.25	0	68
18	0.15	0.10	0.132	69
19, 27, 33	0.20	0.05	0.176	70
20, 29	0.10	0.15	0.088	71
28	0.05	0.20	0.044	72

In a second set of experiments at constant methylammonium chloride concentration, the buffer ratio was changed. The buffer concentration in the exchanging medium was 0.187 M N-methylmorpholine and 0.075 M N-methylmorpholinium perchlorate. The initial buffer concentration was 0.480 M N-methylmorpholine and 0.176 M N-methylmorpholinium perchlorate. The methylammonium chloride concentration was varied from

0.035 M to 0.176 M at a constant ionic strength of 0.25. The same technique as used before was followed with the exception that 0.50 ml of 0.55 M isobutyraldehyde-2-d solution was used making the total volume, 1.25 ml. Table 7 is a tabulation of the experimental details.

Table 7. Constant Buffer Concentration Deuterium Exchange Experiments at Ionic Strength 0.25

0.187 M N-Methylmorpholine 0.22 M Isobutyraldehyde-2-d

0.075 M N-Methylmorpholinium Perchlorate

Experiment No. 2c	Milliliter 0.88 M $MeNH_3Cl$	Milliliter 0.88 M $NaClO_4$	Final Concentration $MeNH_3Cl$	Table Number
21	0.05	0.20	0.035	73
22	0.10	0.15	0.070	74
23	0.25	0	0.176	75
24	0.20	a	0.128	76
25	0.20	0.05	0.128	77

[a] 0.05 ml. of a 3.2 M sodium perchlorate solution to make the ionic strength 0.34.

In the third group of experiments the concentration of methylammonium chloride remained the same and the concentration of the buffer was varied. To prepare the samples for study, 0.25 ml. of 0.88 M methylammonium chloride and a total volume of 0.50 ml. of 0.422 M N-methylmorpholine--0.363 M N-methylmorpholinium perchlorate buffer and

0.363 M sodium perchlorate were injected into an n.m.r. sample tube. At zero time 0.25 ml of 0.55 M isobutyraldehyde-2-d solution was added and the samples placed in a 35° bath as before. Table 8 is a summary of the individual experiments.

Table 8. Constant Methylammonium Chloride Concentration Experiments at Ionic Strength 0.40

0.22 M Methylammonium Chloride

Experiment No. 2c	Milliliter		Final Concentration		Table Number
	Buffer	0.363 M $NaClO_4$	B[a]	BH^+	
4, 9	0.40	0.10	0.169 M	0.145 M	78
5	0.30	0.20	0.127 M	0.109 M	79
6	0.20	0.30	0.084 M	0.073 M	80
7	0.50	0	0.211 M	0.182 M	81
8	0.50[b]	0	0.154 M	0.424 M	82
10	0.25	0.25	0.106 M	0.091 M	83
30	0.40[c]	0.10[c]	0.167 M	0.168 M	84
31	0.30[c]	0.20[c]	0.125 M	0.126 M	85

a. B is N-methylmorpholine concentration.

b. In this experiment a buffer composed of 0.308 M N-methylmorpholine--0.848 M N-methylmorpholinium perchlorate was used.

c. In this experiment a buffer composed of 0.422 M N-methylmorpholine--0.424 M N-methylmorpholinium perchlorate was used. The sodium perchlorate was 0.424 M.

Determination of pK_B Values for Some Amines

The pK_B values were determined for N,N,N',N'-tetramethylethylenediamine, N-methylmorpholine, β-dimethylaminoethanol, triethylenediamine and N-methylmorpholine by titration using a pH meter. The samples were weighed into a 50 ml. beaker and 25 ml. of distilled water was added. The pK of each amine was determined at two ionic strengths. The ionic strength was considered to be the ionic strength of solution being titrated half way to the endpoint. The pK_a was considered to be the pH of the solution half way to the endpoint. The solutions were stirred with a magnetic stirrer, but the stirrer was stopped when a pH measurement was being made. The temperature of the solutions ranged from 25.5° to 27°. The pK_B values were determined by extrapolating to zero ionic strength a plot of the pK_B versus the ionic strength. The extrapolations in all cases except triethylenediamine were less than 0.02 pK_a units. In the case of triethylenediamine the extrapolation was 0.067 pK_a units. Table 9 is a compilation of the experimental data.

Table 9. pK_a Determination Experimental Data

Compound	Weight Grams	Endpoint [a] ml. $HClO_4$ Used 0.0182 M	0.180 M	pH [b]
N-Methylmorpholine	0.0519	24.50		7.45
N-Methylmorpholine	0.1140		5.90	7.44
Triethylenediamine	0.0456	22.50		8.74
Triethylenediamine	0.1088		5.20	8.81
β-Dimethylaminoethanol	0.0517	30.50		9.23
β-Dimethylaminoethanol	0.1108		6.62	9.27
N-Methylimidazole	0.0459	29.50		7.07
N-Methylimidazole	0.1149		7.62	7.09
N,N,N',N'-Tetramethylethylenediamine	0.0513	21.20		9.14
N,N,N',N'-Tetramethylethylenediamine	0.1076		4.75	9.17

[a] The 0.180 M perchloric acid was measured with a 10-ml. burette graduated in 0.05 ml. units. The 0.0182 M perchloric acid was measured with a 50-ml. burette graduated in 0.10 ml. units.

[b] pH at half-equivalence point of titration.

CHAPTER III

RESULTS AND DISCUSSION

Acid Strength of Isobutyraldehyde Hydrate

Aldehydes can behave as weak acids by the addition of hydroxyl ions to give the conjugate base of the hydrate.

$$R\text{-}CHO + OH^- \rightleftarrows R\text{-}CH(OH)O^-$$

$$RCH(OH)O^- + H^+ \rightleftarrows RCH(OH)_2$$

In aqueous solutions of isobutyraldehyde there is an equilibrium amount of the isobutyraldehyde hydrate present. Bell and McTigue (42) have noted that the actual concentration of hydroxide ion in basic solutions of aldehyde is not the formal concentration, but a lesser value due to the reaction of some of the hydroxide ion with the aldehyde hydrate.

$$RCHO + H_2O \rightleftarrows RCH(OH)_2 \qquad K_1$$

$$RCH(OH)_2 + OH^- \rightleftarrows RCH(OH)O^- + H_2O \qquad K_2$$

If these equations are combined,

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42. R. P. Bell and P. T. McTigue, J. Chem. Soc., 1960, 2983.

$$RCHO + OH^- \rightleftarrows RCHOH(O^-) \qquad K_1K_2$$

an equilibrium is obtained that indicates the use of hydroxide ion. Since the value of K_1 is known for the isobutyraldehyde-isobutyraldehyde hydrate system at 25° from the present work to be 0.604, the determination of K_1K_2 would yield the dissociation constant for the isobutyraldehyde hydrate.

The actual concentrations of aldehyde and anion of the hydrate can be determined by examining the ultraviolet spectra of isobutyraldehyde in aqueous solution. On the addition of hydroxide ion to an isobutyraldehyde solution the optical density of the 285 mμ peak drops in a direct relationship to the amount of the conjugate base of the isobutyraldehyde hydrate formed. The O. D. of a 0.1179 M isobutyraldehyde solution (1 centimeter cell) is 1.465. The O. D. of a solution initially 0.1179 M in total isobutyraldehyde and 0.0964 M in sodium hydroxide (1 centimeter cell) is 1.385.

The equilibrium concentration of free isobutyraldehyde is 0.0695 M and the concentration of conjugate base is 0.00644 M. The final concentration of the hydroxide is equal to the initial concentration, 0.0964 M, less the amount used in forming the conjugate base, 0.00644 M, resulting in the final concentration of hydroxide being 0.0900 M. From the extinction coefficients of total isobutyraldehyde, 12.43, and isobutyraldol, 24.43, it can be seen that if aldolization takes place that there will be little change in the optical density. If the equilibrium amount of aldol (0.005 M) is formed, the dissociation constant will be in error by 8 per cent.

$$K_1K_2 = \frac{[(CH_3)_2\overset{H}{\overset{|}{C}}CH(OH)O^-]}{[(CH_3)_2CHCHO][OH^-]} = \frac{[.00644]}{[.0695][.090]}$$

$$K_2 = \frac{[(CH_3)_2CH(OH)O^-]}{[(CH_3)_2CHO][OH^-]} \cdot \frac{1}{0.604}$$

$$K_2 = 1.708$$

From these values the dissociation constant, K_A, for isobutyraldehyde hydrate will be 1.71×10^{-14}. This value is near with the values for acetaldehyde hydrate and formaldehyde hydrate reported by Bell and Onwood (43).

In order to relate the value of the dissociation constant of isobutyraldehyde hydrate with the acid strength of other alcohols a Taft correlation can be made. The values for the dissociation constants of several alcohols and hydrates are listed in Table 10 along with the total σ* for the compounds.

Table 10. Substituent Effects for Ionization of R_3COH

Compound	pK_A [a]	$\Sigma\sigma^*$
$\phi\text{-}\overset{CF_3}{\overset{|}{C}}\text{-}(OH)_2$	10.00 (44)	4.75
$Cl_3C\text{-}CH(OH)_2$	10.04 (46)	4.71

43. R. P. Bell and D. P. Onwood, J. Chem. Soc., 1962, 1557.

[a] Not statistically corrected.

Table 10. Substituent Effects for Ionization of R_3COH (Continued)

Compound	pK_A [a]	$\Sigma\sigma^*$
ϕ-$CH(CF_3)OH$	11.90 (44)	3.67
CCl_3CH_2OH	12.24 (45)	3.63
CF_3CH_2OH	12.37 (45)	3.56
$CHCl_2CH_2OH$	12.89 (45)	2.92
$CH{\equiv}C\text{-}CH_2OH$	13.55 (45)	2.68
$H_2C(OH)_2$	13.27 (46)	2.55
$CH_3CH(OH)_2$	13.57 (46)	2.16
$ClCH_2\text{-}CH_2OH$	14.31 (45)	2.03
$Me_2CHCH(OH)_2$	13.77 [3]	1.87
$CH_3O\text{-}CH_2CH_2OH$	14.8 (45)	1.62
$HOCH_2\text{-}CH_2OH$	14.8 (45)	1.54
HCH_2OH	15.09 (47)	1.47
CH_3CH_2OH	15.93 (47)	0.98

[a] Not statistically corrected.

44. R. Stewart and R. Van der Linden, Can. J. Chem., 38, 399 (1960).

45. P. Ballinger and F. A. Long, J. Am. Chem. Soc., 82, 795 (1960).

46. R. P. Bell and D. P. Onwood, Trans. Faraday Soc., 58, 1557 (1962).

[3] From this work.

47. J. Murto, Ann. Acad. Sci. Fenniaue, A. II, 117 (1962).

In the case of the hydrates and ethylene glycol, it is necessary to add to the observed pK_A values log 2 to account for the two possible reaction sites (48). Evaluations of σ^* for trifluoromethyl and hydroxy radical had to be made. As an approximation the value of the σ^* value of the radical was assumed to be equal to 2.8 times the σ of 0.92 and the $HOCH_2$- has a value of 0.56. The σ values for the trifluoromethyl and the hydroxyl radical are 2.58 and 1.57, respectively.

Fig. 2 is a plot of $\Sigma\sigma^*$ versus the pK_A of the compound. A value of 1.44 is obtained for ρ^* which compares well with the value of 1.42 obtained by Ballinger and Long (45) and the value of 1.36 calculated by Taft (50) for alcohols from the work of Hine and Hine (51).

Dealdolization of Isobutyraldol

In order to study the base-catalyzed dealdolization of isobutyraldol it was necessary to analyze the nuclear magnetic resonance spectra of isobutyraldehyde and isobutyraldol to obtain the concentrations of these compounds at various times during the reaction. The technique used to determine the extent of exchange in the kinetics studies was to prepare a series of synthetic mixtures and draw a calibration curve. The technique used in this study is an analysis of the nuclear magnetic resonance spectra.

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48. S. W. Benson, J. Am. Chem. Soc., 80, 5151 (1958).

49. M. S. Newman, ed., Steric Effects in Organic Chemistry, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 592.

50. R. W. Taft, Jr., J. Am. Chem. Soc., 75, 4231 (1953).

51. J. Hine and M. Hine, J. Am. Chem. Soc., 74, 5266 (1952).

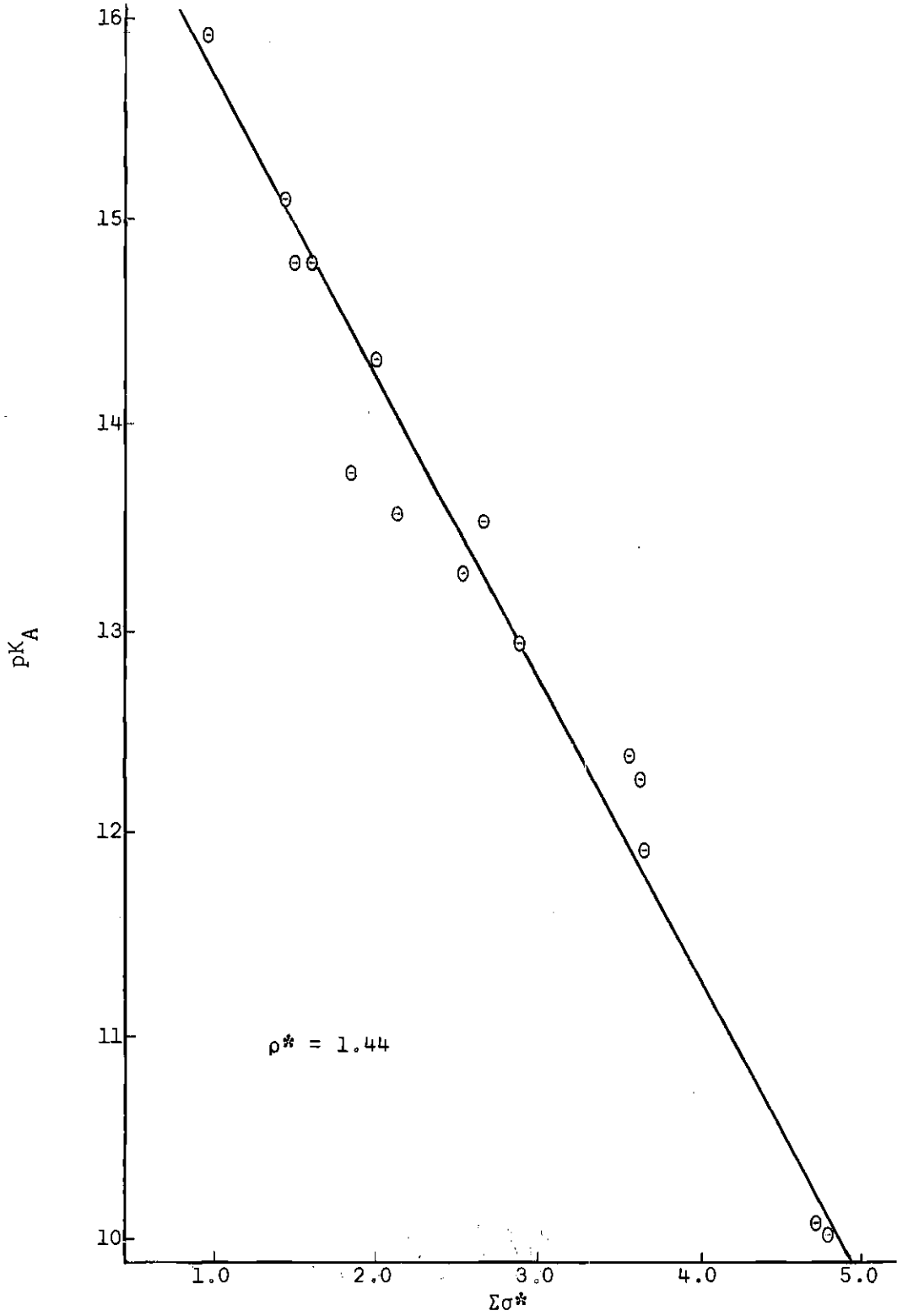

Figure 2. Taft Plot of $\Sigma\sigma^*$ vs. the pK_A of a Group of Compounds, R_3COH

It would seem that if it were possible to determine the concentration of protons causing a peak or group of peaks, then one could determine the concentration of the compound. This would follow from the assumption that the area of a nuclear magnetic resonance signal is proportional to the concentration of protons in a particular environment. Then some proportionality constant, N_o, multiplied by the signal area should give the concentration of nuclei under a given set of conditions (52). In the case of isobutyraldol the hydrogens in the two δ-methyl groups produce a sharp singlet at 8.92τ. As discussed previously in Part I, the area of the signal is the product of the width of the signal at half-height and the height of the signal.

The area of the 8.92τ peak from the δ-methyl groups in isobutyraldol in water is proportional to the number of protons causing the singlet (6) and the concentration of isobutyraldol $[(IBA)_2]$ assuming there is no hydrate formed. If the proportionality constant is N_o, the area is:

$$[\text{Area}]_{8.92\tau} = 6N_o[(IBA)_2]$$

In the case of isobutyraldehyde the situation is slightly more complicated because the δ-methyl groups are split into a doublet and the aldehyde is partially hydrated. The area of the 8.58τ peak of the doublet of the Me_2CH-group is proportional to the number of protons causing the doublet (6), the fraction of the total area of doublet in the 8.58τ

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52. J. D. Roberts, Nuclear Magnetic Resonance, McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 30.

peak (0.54), the total isobutyraldehyde concentration $[IBA]_T$ and the fraction of the aldehyde present as free aldehyde (0.70).

$$[Area]_{8.58\tau} = 6N_o(0.54)(0.70)[IBA]_T$$

The kinetics of a pseudo-first order reaction follow the form:

$$kt = \ln[\frac{(IBA)_2^0}{(IBA)_2^0-x}]$$

in the dealdolization of isobutyraldol, where x is the amount of alcohol reacted.

$$(IBA)_2 \rightarrow 2(IBA)$$

Therefore, at any time

$$[(IBA)_2^0] = [IBA]_2 + 1/2[IBA]_T$$

The form of the kinetic equation becomes

$$kt = \ln[\frac{[(IBA)_2] + 1/2[IBA]_T}{[(IBA)_2]}]$$

or

$$kt = \ln[\frac{6N_o[B]}{6N_o[A] + 1/2\ \overline{(0.54)(0.70)}}] \qquad (1)$$

where B and A represent the areas of signal due to the 8.58τ peak of

isobutyraldehyde and the 8.92τ peak of isobutyraldol, respectively.

To study the kinetics using Equation 1 attempts were made to add dilute sodium hydroxide to isobutyraldol solution and follow the dealdolization. However, in unbuffered solutions small amounts of oxidation made the study impossible. Buffers of triethylenediamine and trimethylamine were used and both give the same value within experimental error. The value of the second-order rate constant for the trimethylamine-buffered experiment would fall at 6.50 $l.-m.^{-1}-sec.^{-1}$ if the pK_B value were in error 0.025 units.

Table 11. Dealdolization of Isobutyraldol by Hydroxide Ion

Buffer	[B][a]	[BH]	$k_{obs.} \times 10^4$	[OH]	k_{OH^-} $l.-m.^{-1}-sec.^{-1}$
Triethylenediamine	0.039M	0.00734M	1.55	2.52	6.15
Triethylenediamine	0.0229M	0.0158 M	0.463	0.68	6.82
Trimethyloamine	0.0086M	0.0070 M	4.10	7.76	5.28

a. B is the concentration of the amine in the buffer.

Since the equilibrium constant for the aldehyde-aldol equilibrium is known from other work at 25°, it was possible to estimate the rate constants if the reaction proceeds to an equilibrium concentration. The trimethylamine-buffer kinetics were studied to test this possibility. In this reaction the reactants and products have approached nearer to

their equilibrium values than in the other two cases studied; therefore, a kinetic form that takes the equilibrium into account should show the biggest effect in this case. The values of the second-order rate constant for the reaction is 5.35 $l.\text{-}m.^{-1}\text{-}sec.^{-1}$ using the kinetic equation that considers the equilibrium (53) assuming the equilibrium constant is the same at 35° as at 25°. The second-order rate constant is 5.28 $l.\text{-}m.^{-1}\text{-}sec.^{-1}$ for a simple second-order treatment. Since the equilibrium will probably be shifted even further toward aldehyde at 35° as judged by data obtained using acetone and using isobutyraldehyde in a heterogeneous solution (23, 54), the difference in the two treatments will be even smaller.

The dealdolization of isobutyraldol would be expected to follow a mechanistic path analogous to the one ascribed to the dealdolization of diacetone alcohol (2) and the reverse of the path described for the aldolization of acetaldehyde (55) in which it is assumed that the first step is an equilibrium step (i.e., $k_{-1}[BH^+] >> k_2$).

$$Me_2CH\overset{OH}{C}HCMe_2CHO + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} Me_2CH\overset{O^-}{C}HMe_2CHO + H_2O$$

$$Me_2CH\overset{O^-}{C}HCMe_2CHO \underset{k_{-1}}{\overset{k_2}{\rightleftarrows}} Me_2CHCHO + Me_2\bar{C}CHO$$

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53. A. A. Frost and R. G. Pearson, Kinetics and Mechanisms, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 186.

54. W. Herold, Z. Physik. Chem., 18B, 265 (1932).

55. J. Hine, Physical Organic Chemistry, 2nd ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, sec. 11-3b.

$$Me_2\bar{C}CHO + BH^+ \underset{k^H_B}{\overset{k_{BH^+}}{\rightleftarrows}} Me_2CHCHO + B$$

$$Me_2\bar{C}CHO + H_2O \underset{k^H_{OH^-}}{\overset{k_{H_2O}}{\rightleftarrows}} Me_2CHCHO + OH^-$$

$$Me_2\bar{C}CHO + H_3O^+ \underset{k\omega}{\overset{k_{H^+}}{\rightleftarrows}} Me_2CHCHO + H_2O$$

From studies made during the present work, it has been shown that the attack of water contributes negligibly to the rate of formation of carbanions from isobutyraldehyde under the conditions used in the dealdolization kinetic experiments. From this observation and the principle of microscopic reversibility, it follows that a negligible fraction of the carbanions from isobutyraldehyde are protonated by hydronium ions. Considering the rate-determining step to be irreversible and making the steady state approximation for the intermediate alkoxide ion and carbanion, the rate of disappearance of isobutyraldehyde is:

$$V_d = \frac{k_1 k_2 (k_{BH^+}[BH^+] + k_{H_2O})[OH^-][(IBA)_2]}{k_{-1}(k_{-2}[IBA] + k_{BH^+}[BH^+] + k_{H_2O})} \qquad (2)$$

where $(IBA)_2$ represents the aldol, IBA isobutyraldehyde and BH^+ the acidic component of the buffer.

To get constant first-order rate constants in the dealdolization studies it is necessary that the term, $k_{BH^+}[BH^+] + k_{H_2O}$, be considerably

larger than k_{-2}[IBA], that is to say, the protonation is the usual fate of the isobutyraldehyde carbanions under the conditions used. With this assumption, Equation 2 reduces to:

$$V_d = \frac{k_1 k_2}{k_{-1}} [(IBA)_2][OH^-] \qquad (3)$$

To justify ignoring k_{-2}[IBA] with respect to $k_{BH^+}[BH^+] + k_{H_2O}$, the following calculations can be made. The equilibrium constant for aldolization may be stated,

$$K_a = \frac{k_{-1}k_{-2}k^H_{OH^-}}{k_1 k_2 k_{H_2O}} = \frac{k_{-1}k_{-2}k^H_B}{k_1 k_2 k_{HB} K_B}$$

where K_B is the ionization constant for B.

The rate constant for removal of a proton from isobutyraldehyde by hydroxide ion is not available. In this work, however, the rate constant for deuterium removal by hydroxide was found to be 3.3×10^{-2} l.-m.$^{-1}$-sec.$^{-1}$ The aldolization equilibrium constant is 0.70 and the second-order rate constant for dealdolization, k_1k_2/k_{-1}, is roughly six l.-m.$^{-1}$-sec.$^{-1}$ The term, k_{H_2O}/k_{-2}, can be stated

$$k_{H_2O}/k_{-2} = \frac{(k^H_{OH^-}/k^D_{OH^-})k^D_{OH^-}}{k_1 k_2 K_a / k_{-1}} = 8\times10^{-3}\ (k^H_{OH^-}/k^D_{OH^-})\underline{M} \qquad (4)$$

Using the same technique with the values of k^D_B (6.5×10^{-3} and 1.6×10^{-3} l.-m.$^{-1}$-sec.$^{-1}$, respectively) and pK_B (5.33 and 4.20, respectively) for triethylenediamine and trimethylamine values of $336(k^H_B/k^D_B)$ and 61 (k^H_B/k^D_B), respectively, can be calculated for k_{HB}/k_{-2}. These calcula-

tions show that in the dealdolization studies using triethylenediamine and trimethylamine buffers (even using the least favorable kinetic isotope effect of unity and the least favorable buffer, trimethylamine-trimethylammonium ion) the intermediate carbanion has been protonated more than 9 times out of 10 at 80 per cent reaction.

However, without a buffer, the situation is somewhat different. According to the results in Equation 4 the dealdolization of 0.0424 M isobutyraldol in the presence of a sodium hydroxide catalyst would result in protonation of carbanions, using $k^{H}_{OH^-}/k^{D}_{OH^-}$ of 6, 50 per cent of the time. If a value for $k^{H}_{OH^-}/k^{D}_{OH^-}$ of unity is used the carbanion is protonated only 14 per cent of the time. This would provide an additional reason why in dealdolization studies with sodium hydroxide the first-order rate constants fell.

Determination of the Isobutyraldehyde-Isobutyraldol Equilibrium Constant

In order to find the equilibrium constant for the reaction

$$2[IBA]_F \rightleftarrows (IBA)_2 \qquad K_a$$

both ultraviolet spectra and nuclear magnetic resonance spectral data were used. This was done because the concentration proportionality constant between actual concentration and signal area will not cancel out as it did in the kinetics of dealdolization expression. The ratio of the concentration of isobutyraldehyde to isobutyraldol in a saturated solution at 25° can be obtained from the nuclear magnetic resonance

spectrum which was made at 35°. The aldehyde-aldol equilibrium was frozen by adding acetic acid to neutralize the base. The ratio of total isobutyraldehyde to isobutyraldol should be the same at 25° and 35°. However, the free isobutyraldehyde concentration will vary depending on the degree of hydration. Since the per cent hydration of isobutyraldehyde is known at both temperatures and the aldol is not detectably hydrated, the concentration of free isobutyraldehyde can be determined at 25° from the nuclear magnetic resonance data at 35°.

From the section on dealdolization the total isobutyraldehyde concentration at 35° is:

$$[IBA]_T = \frac{6N_o[.B]}{(.541)(.70)}$$

The concentration of isobutyraldol is:

$$[(IBA)_2] = 6N_o[A]$$

where B and A are the areas of the 8.58τ isobutyraldehyde signal and the 8.92τ isobutyraldol signal, respectively. The ratio of total isobutyraldehyde to isobutyraldol at 35° is

$$\frac{[IBA]_T}{[(IBA)_2]} = \frac{2.64[B]}{[A]}$$

From the nuclear magnetic resonance data at 35° the ratio is then 17.84. From ultraviolet data at 25°, the absorbance of the saturated aldol-aldehyde solution is 1.440. In the equilibrium it is necessary to use

the free aldehyde concentration which is the product of the per cent free aldehyde and the total aldehyde concentration. An aqueous isobutyraldehyde solution contains 62 per cent free aldehyde. The ultraviolet absorbence is equal to the following:

$$19.93[IBA]_F + 24.78[(IBA)_2] = 1.440$$

where

$$[IBA]_T = 17.84\ [(IBA)_2] \text{ and } [IBA]_F = [IBA]_T\ .62$$

Then $[IBA]_F$ or the free aldehyde concentration is 0.0646 M and the isobutyraldol concentration is 0.00587 M. Since the solutions used were diluted 1:1 with distilled water the concentrations of the saturated solution are twice those given above or

$$\frac{[(IBA)_2]}{[IBA]_F^2} = 0.70$$

at 25°.

Deuterium Exchange Kinetics at 35° C

Before a general discussion can be made of the various catalytic rate constants obtained for the various compounds in the deuterium exchange experiments, it is necessary to look at the corrections that were made on the observed first-order rate constants. Then it will be

possible to look at the relationship or Bronsted Law plot between the log of the catalytic rate constant and the pK_B. From this plot certain conclusions can be drawn concerning the exchange reaction.

There are two general difficulties in the study of the exchange reaction using these catalysts. In the cases where very hindered bases were studied in the pyridine series, 2,6-dimethylpyridine and 2,4,6-trimethylpyridine--the compounds could be used only at the very low concentration because of the limited solubility of the amines in water. This means that the study would have taken weeks. In most of the studies, the experiments lasted no longer than one week. After about two weeks, the isobutyraldehyde-2-d begins to be oxidized enough due to leakage through the plastic caps to cause serious concern. For this reason, the values given for the very slow hindered amine represents a maximum value of the rate. The second difficulty is encountered with the very strong bases as has been mentioned before. The aldol condensation is rapid in the stronger bases. To avoid this complication very dilute amine buffers must be used. This means that to obtain the concentration of free amine, it is necessary in relative terms to subtract one large number, the isobutyric acid concentration from another, the initial amine concentration to obtain a small number, the final amine concentration. This trouble was minimized by titrating samples of the reacting mixture several times during a kinetic experiment. Also, these strong bases promoted fast exchange which meant only short periods of time were available for the study. The solutions would begin to cloud if trimerization became a problem.

In the case of the acetic acid buffer study the kinetics were run at two buffer ratios to learn whether the anion and/or the free acid were catalyzing the reaction. The two experiments gave reasonable agreement when the acetic acid concentration was completely ignored.

Table 12. Acetic Acid-Acetate Ion Kinetics at Two Buffer Ratios

Acetic Acid	Acetate	$k_{obs} \times 10^7$ $sec.^{-1}$	$k_{cat} \times 10^7$ $l.\text{-}m.^{-1}\text{-}sec.^{-1}$
0.156 M	0.833 M	7.40	8.67
0.319 M	0.319 M	3.00	8.83

Hydroxide Ion-Catalyzed Deuterium Exchange Term

The rates have been corrected for hydroxide ion, water, and isobutyrate ion-catalysis. In the experiments that involve ineffective catalysts the very small amount of hydroxide ion catalysis becomes noticeable. In the case of the acetate exchange study the correction amounted to less than 1 per cent.

To correct for hydroxide ion catalysis, all the experiments were made in the following way. The hydroxide ion concentration was obtained from the following equation in all cases

$$K_B = \frac{[BH^+][OH]}{[B]}$$

where [B] is the base in question and $[BH^+]$ is the conjugate acid of

that base. The values of [B] and [BH^+] used were in most cases corrected on the assumption that the isobutyric acid was completely neutralized. This assumption was checked with several of the weak bases and with the exception of acetate ion, pyridine, and trimethylamine-N-oxide cases the isobutyric acid was over 90 per cent neutralized. The compounds were corrected for the actual amount neutralized. Table 13 indicates the magnitude of the corrections made for hydroxide ion catalysts. When the correction was negligible the amine is not listed.

In no case is the hydrogen ion-catalyzed exchange term large enough to consider because the combination of a low rate constant and a low hydrogen ion concentration make the term negligible.

Table 13. Correction for Hydroxide Ion Catalysis

Experiment Number	Compound	$[OH]\times10^6$	$k_{OH}[OH]\times10^8$ $l.\text{-}m.^{-1}\text{-}sec.^{-1}$	k_{ob} $l.\text{-}m.^{-1}\text{-}sec.^{-1}$
18	2,4-Lutidine	1.21	4.03	1.85×10^{-6}
19	Phenol	71.9	23.73	4.61×10^{-5}
20	β-Dimethylaminoethanol	24.8	81.84	2.73×10^{-5}
21	Triethylamine	152.0	509.0	1.56×10^{-5}
22	m-Chlorophenol	9.44	31.15	1.9×10^{-5}
23	p-Chlorphenol	17.1	56.43	5.13×10^{-5}
24	m-Nitrophenol	1.15	3.795	4.08×10^{-6}
26	p-Cresol	95.2	314.2	8.03×10^{-5}
27	Phenol	87.9	290.1	5.25×10^{-5}
28	N-Methyldiethylamine	68.1	224.7	1.38×10^{-4}

Table 13. Correction for Hydroxide Ion Catalysis (Continued)

Experiment Number	Compound	$[OH]\times10^{6}$	$k_{OH}[OH]\times10^{8}$ $l.-m.^{-1}-sec.^{-1}$	k_{ob} $l.-m.^{-1}-sec.^{-1}$
35	2,4,6-Trimethylpyridine	0.16	.528	1.1×10^{-7}
36	2,6-Dimethylpyridine	0.024	.0792	8.55×10^{-8}
37	o-Cresol	63.5	209.6	5.45×10^{-5}
42	Triethanolamine	0.984	3.247	9.11×10^{-7}
47	N-Methylpyrrolidine	154.0	508.2	1.18×10^{-4}
48	N-Methylpiperidine	118.0	389.4	2.63×10^{-5}

To obtain the catalytic rate constant for hydroxide ion it was necessary to consider the acidity of the isobutyraldehyde hydrate. Bell and McTigue (1) have found in their study of the aldolization of acetaldehyde that to obtain the actual hydroxide concentration in an aqueous aldehyde solution the hydrate acidity must be considered. The ionization constant of isobutyraldehyde hydrate has been determined in this work to be 1.71×10^{-14}. To correct the hydroxide ion concentration the following equilibrium must be considered.

$$[IBA]_F + H_2O \rightleftarrows [IBAOH_2] \qquad K_{Hy}$$

$$[IBAOH_2] + [\bar{O}H] \rightleftarrows [IBAOH^-] + H_2O \qquad K_I$$

From Part I, the value of the hydration equilibrium constant is 0.423 at 35°. Therefore

$$\frac{K_A K_{Hy}}{K_w} = 0.764$$

To determine the final hydroxide ion concentration the following method is used

$$\frac{[IBAOH^-]}{[IBA]_F[OH]} = 0.764$$

The hydroxide concentration is the initial hydroxide ion concentration minus the concentration of isobutyraldehyde hydrate anion.

The corrections for the acidity of the isobutyraldehyde hydrate is negligible in all the studies made except the hydroxide ion catalyzed exchange.

Table 14. Correction to Hydroxide Ion Concentration for Acidity of Hydrate

Initial [OH]	$[IBAOH^-]$	Final [OH]
0.00369 M	0.0005 M	0.00319 M
0.00855 M	0.00116 M	0.00749 M
0.0192 M	0.00260 M	0.0166 M

The second-order rate constant for deuterium exchange from isobutyraldehyde-2-d is equal to the slope of the line formed by the plot of the observed first-order rate constants for deuterium exchange from

isobutyraldehyde-2-d versus the concentration of hydroxide ion, Fig. 3. The value of the second-order rate constant is 0.0333 $l.\text{-}m.^{-1}\text{-}sec.^{-1}$ These calculations yield a maximum value for the hydroxide ion catalysis since it is assumed that the anion of isobutyraldehyde hydrate is not a catalyst.

Determination of Water-Catalyzed Exchange Rate

Since the water-catalyzed rate of catalysis is very slow at 35°, the exchange of isobutyraldehyde-2-d was studied in 0.0048 M acetate ion at 60° and 100° and from the energy of activation, the water-catalyzed rate of exchange was approximated at 35°. At 60° the observed rate constant for exchange was 2.75×10^{-7} $sec.^{-1}$ and at 100°, $7.30 \times 10^{-6} sec.^{-1}$ The energy of activation obtained from the data at 60° and 100° is 20.2 kcal/mole. Using this value the first-order rate constant for exchange at 35° is $2.3 \times 10^{-8} sec.^{-1}$

The second-order rate constant for isobutyrate ion catalysis was approximated for the Bronsted plot, Fig. 4, in the following manner. Assuming that there is a Bronsted plot for carboxylate ion catalysis and that acetate ion falls on this plot, the slope of the plot can be taken to be the slope of the phenoxide plot, 0.532. Using this calculation, the second-order rate constant for isobutyrate ion catalysis is 9.8×10^{-7} $l.\text{-}m.^{-1}\text{-}sec.^{-1}$ Even if the slope of the carboxylate plot differs from that of the phenoxide, the extrapolation is short enough to make the difference in slope inconsequential.

The contribution of each of the catalysts in the acetate ion solution used to determine the activation energy in in Table 15. The

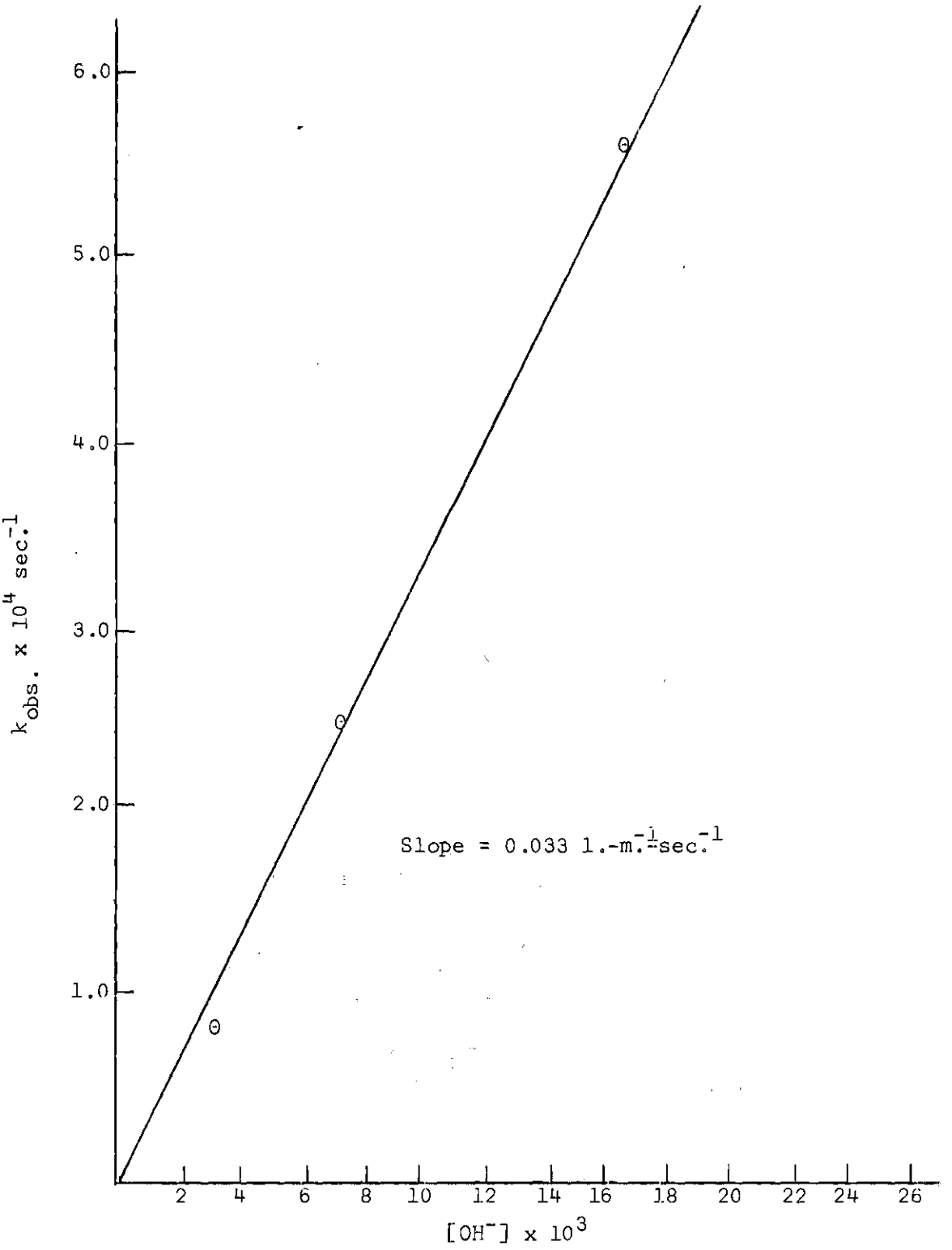

Figure 3. Plot of the Hydroxide Ion Concentration vs. the First-Order Rate Constant for Deuterium Exchange

difference between the rate calculated from the activation energy and the rate due to the tabulated catalysts is attributed to catalysis by water. At 35° the water term is then 1.8×10^{-8} sec.$^{-1}$

Table 15. Contributions of Various Catalysts to Deuterium Exchange Rate

Catalyst	Concentration Moles/Liter	k l.-m.$^{-1}$-sec.$^{-1}$	k[Con.] sec.$^{-1}$
Hydrogen Ion	1.8×10^{-5}	3.15×10^{-5}	5.8×10^{-10}
Hydroxide Ion	5.5×10^{-5}	3.33×10^{-2}	1.8×10^{-11}
Acetate Ion	2.4×10^{-3}	8.76×10^{-7}	2.1×10^{-9}
Isobutyrate Ion	2.4×10^{-3}	9.8×10^{-7}	2.4×10^{-9}

This calculation requires the assumption that the first-order rate constant at 35° for this reaction, which proceeds by several different paths, be that calculated from the Arrhenius activation energy and the first-order rate constants at 60° and 100°. The errors in calculation are small enough, however, to make the determination meaningful. The rate constants for inefficient catalysts are the only ones affected by the water-catalyzed exchange.

pK_B Values for Amines Determined in this Work

Some of the pK_B values needed in this study were not available in the literature. Table 16 is a compilation of the pK_B values (extrapolated to zero ionic strength) determined in this study. The liter-

ature values quoted are generally measurements made at only one ionic strength.

Table 16. Zero Ionic Strength pK_B Values for Some Amines

Amine	pK_B Determined	pK_B Literature	
N-Methylmorpholine	6.55	6.59	(56)
Triethylenediamine	5.33	5.40	[4]
β-Dimethylaminoethanol	4.79		[5]
N-Methylimidazole	6.94	7.00	(57)
N,N,N',N'-Tetramethylethylenediamine	4.87	5.03	(37)

Isobutyrate Ion-Catalyzed Deuterium Exchange

During the study there were five exchange studies that went slowly enough to necessitate the consideration of deuterium exchange catalysis by isobutyrate ion. Using the value for the second-order rate constant for isobutyrate ion catalyzed deuterium exchange approximated in the previous section, 9.8×10^{-7} l.-m.$^{-1}$-sec.$^{-1}$, term can be ignored in all but the very slow exchange studies. Table 17 is a compilation of the corrections necessary in these cases.

56. H. K. Hall, J. Phys. Chem., 60, 63 (1956).

57. M. L. Bender and B. W. Turnquest, J. Am. Chem. Soc., 79, 1656 (1957).

[4] Data provided by the Houdry Process Corporation.

[5] No value found in the literature.

Table 17. Isobutyrate Ion-Catalyzed Deuterium Exchange Term

Compound	Isobutyrate Ion M x 10^2	k[Isobutyrate Ion] x 10^8 $sec.^{-1}$
2,4,6-Trimethylpyridine	2.2	2.2
2,6-Dimethylpyridine	2.2	2.2
Triethanolamine	0.8	0.78

Second-Order Rate Constants for Deuterium Exchange of Isobutyraldehyde-2-d

A compilation of the kinetic data on catalysts studied in the deuterium exchange of isobutyraldehyde-2-d is made in Tables 18 and 19. In all cases except where previously noted, the concentration of isobutyric acid has been considered in determining the concentration of base and its conjugate acid.

The catalytic rate constants have all been calculated considering the contribution of hydroxide ion-catalyzed term, the water-catalyzed term and the isobutyrate ion-catalyzed term as described before. Figure 4 is a Bronsted plot of the ionization constants and the catalytic rate constants. The pK_B values are thermodynamic constants at 25°. The K_B values used are not equal to $[BH^+][OH^-]/[B][H_2O]$ but are equal to 55.5 (the concentration of water in an aqueous solution) times this; namely, $[BH^+][OH^-]/[B]$. Multiplication by 55.5 will not change the shape of the Bronsted plot, but will permit the convenience of using K_B values of the kind ordinarily employed for bases.

The equation for water takes the form

$$H_2O + H_2O \rightleftarrows H_3O^+ + OH^-$$

Multiplication of the equilibrium constant for this process by the water concentration shows the K_B to be $K_w/[H_2O]$.

According to Benson (48) symmetry corrections on equilibrium or rate constants are made by multiplying the experimental value by the product of the symmetry numbers of the products of the reaction divided by the product of the symmetry number of the reactants. Therefore K_B for water is multiplied by 3/2 and K_B for hydroxide ion by two. The catalytic constant for water is multiplied by 2/2 and that for hydroxide by one. In the case of N,N,N',N'-tetramethylethylenediamine, triethylenediamine and acetate ion the K_B values are multiplied by 1/2 and the catalytic constants are multiplied by 1/2.

The Bronsted plot indicates a lack of agreement with the Bronsted Law at first glance. The disagreement of various types of amines with the Bronsted Law has been discussed by Bell (58). Usually this disagreement involved the separation of the points for primary, secondary and tertiary amines into three different lines. Bell believes this is due to solvation. In the series of amines studied, all were tertiary amines, but amines with both sp^2 and sp^3 hybridized nitrogen atoms were studied. It appears, however, that steric hindrance causes a much larger

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58. R. P. Bell, The Proton in Chemistry, Cornell University Press, Ithaca, N. Y., 1959, p. 175.

deviation from the linear free energy relationship than the difference in hybridization. From a look at the Bronsted plot, it would seem that the unhindered pyridines and some of the alkyl amines with one or two methyl groups attached to nitrogen correlated. This may be due to combinations of electronic and steric effects.

Table 18. Second-Order Rate Constants for Deuterium Exchange

Compound	k_{cat} $l.\text{-}m.^{-1}\text{-}sec.^{-1}$	pK_B	
Sodium p-Cresolate	2.81×10^{-3}	3.74	(62)
Sodium o-Cresolate	2.16×10^{-3}	3.71	(62)
Sodium Phenoxide	1.65×10^{-3}	4.00	(62)
Sodium p-Chlorophenoxide	1.25×10^{-3}	4.58	(62)
Sodium m-Chlorophenoxide	6.80×10^{-4}	4.87	(62)
Sodium o-Chlorophenoxide	3.35×10^{-4}	5.47	(62)
Sodium m-Nitrophenoxide	2.83×10^{-4}	5.62	(62)
Sodium p-Nitrophenoxide	5.12×10^{-5}	6.85	(62)
Trimethylamine-N-Oxide	5.26×10^{-6}	9.35	(67)
Sodium Acetate	8.76×10^{-7}	9.24	(60)
Sodium Hydroxide	3.33×10^{-2}	-2.05	
Water	3.2×10^{-10}	15.57	
Perchloric Acid	3.15×10^{-5}		

Table 19. Second-Order Rate Constants for Deuterium Exchange

Compound	k_{cat} $l.\text{-}m.^{-1}\text{-}sec.^{-1}$	pK_B	
Trimethylamine	1.60×10^{-2}	4.20	(59)
N-Methylpyrrolidine	7.64×10^{-3}	3.54	(35)
N-Methyldiethylamine	7.27×10^{-3}	3.71	(64)
Triethylenediamine	6.48×10^{-3}	5.63	6
N-Methylpiperidine	1.45×10^{-3}	3.92	(35)
N,N,N',N'-Tetramethylethylenediamine	1.39×10^{-3}	5.17	6
β-Dimethylaminoethanol	9.43×10^{-4}	4.79	6
Triethylamine	7.72×10^{-4}	3.25	(63)
N-Methylmorpholine	1.83×10^{-4}	6.56	6
N-Methylimidazole	1.59×10^{-5}	6.94	6
Triethanolamine	3.62×10^{-6}	6.23	(66)
3,4-Lutidine	3.19×10^{-5}	7.54	(61)
4-Picoline	1.55×10^{-5}	8.02	(61)
2,4-Lutidine	1.06×10^{-5}	7.37	(61)
Pyridine	7.89×10^{-6}	8.78	(61)
2,4,6-Trimethylpyridine	7.3×10^{-7}	6.55	(65)
2,6-Dimethylpyridine	2.7×10^{-7}	7.28	(61)

59. D. H. Everett and W. F. K. Wynne-Jones, Proc. Roy. Soc. (London), A177, 499 (1941).

[6] Determined in this work.

60. E. Grunwald and B. J. Berkowitz, J. Am. Chem. Soc., 73, 4939 (1951).

61. R. J. L. Andon, J. D. Cox and E. F. G. Herington, Trans. Faraday Soc., 50, 918 (1954).

62. A. I. Biggs and R. A. Robinson, J. Chem. Soc., 1961, 388.

63. N. F. Hall, J. Am. Chem. Soc., 52, 5115 (1930).

64. J. Hansson, Svensk Kem. Tidskr., 67, 256 (1955).

65. A. Gero and J. J. Markham, J. Org. Chem., 16, 1835 (1951).

66. R. G. Bates and G. Schwarzenbach, Helv. Chim. Acta, 37, 1437 (1954).

67. P. Nylén, Z. Anorg. Allgem. Chem., 246, 227 (1941).

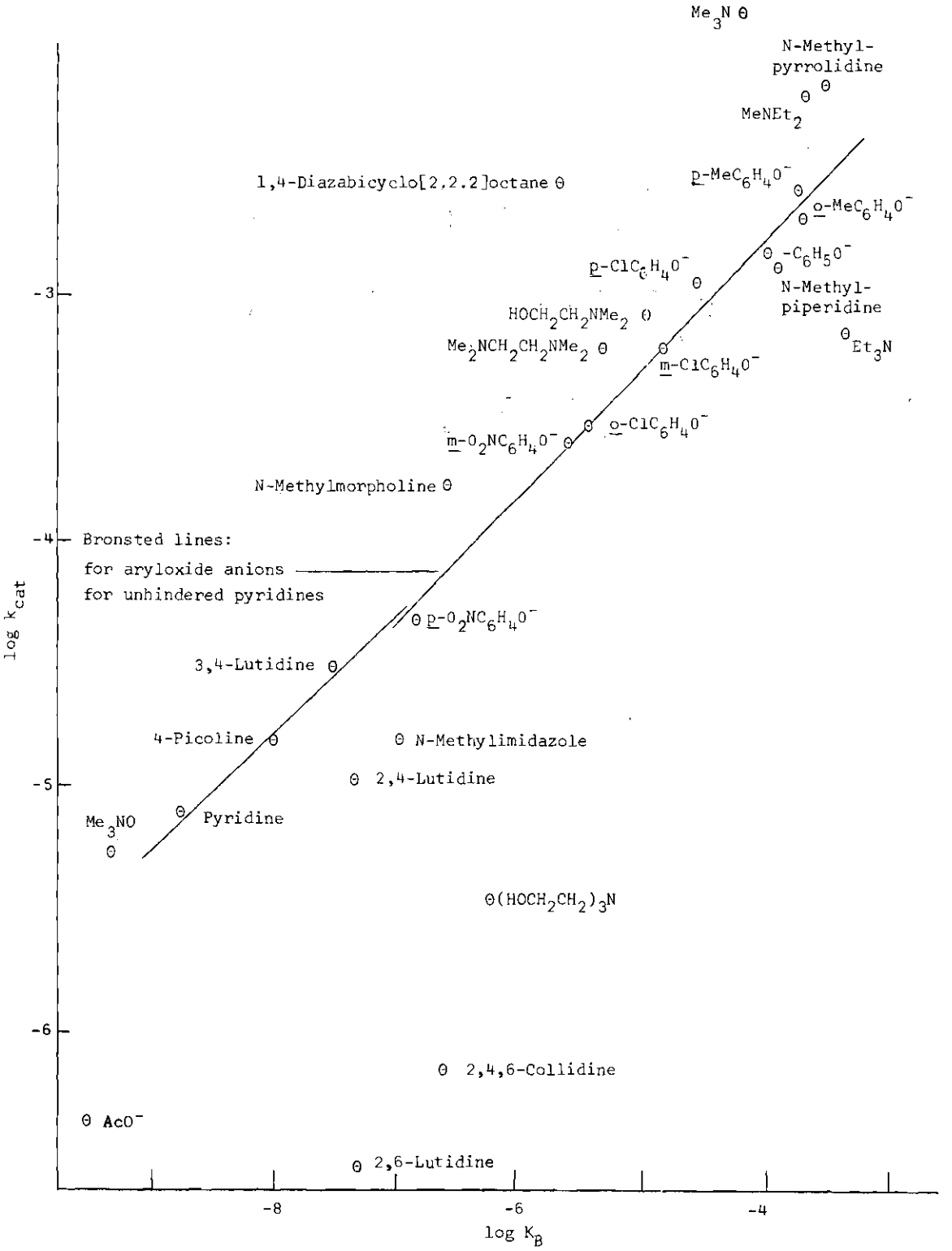


Figure 4. Plot of Log K_B *vs.* Log Second-Order Rate Constant for Deuterium Exchange from Isobutyraldehyde-2-d by Various Bases

However, in one case, the pyridines and imidazole, the electronic configuration is the same. This gives an opportunity to look at the steric hindrance. In the case of pyridine, 4-picoline and 3,4-lutidine, there is the same amount of hindrance. These compounds follow the Bronsted Law. As we noted in the introduction, hindered pyridine bases do not follow the Bronsted Catalysis Law in cases where the rate-determining step is proton removal from a hindered position. This deviation from the Bronsted equation can be expressed as $\Delta\log k_c = \log k_c - \log K_B - \log G$ where the values of β and log G are parameters determined from the unhindered pyridine bases--those without 2 and 2,6 substituents.

In the deuterium removal reported in this work 2,6-lutidine and 2,4,6-trimethylpyridine have $\Delta\log k_c$ values of -2.21 and -2.16, respectively. The value of $\Delta\log k_c$ for 2,4-lutidine is somewhat lower, -0.56. The value of -2.21 reported for 2,6-lutidine is the largest deviation reported to date.

From the data of Lewis and Allen (9) a $\Delta\log k_c$ value of -1.16 for 2,6-lutidine-catalyzed iodination of 2-nitropropane and a value of -1.0 for 2,6-lutidine in the case of 2-nitropropane-1-d_2 may be calculated. In agreement with earlier work by Pearson and Williams (7,8) Lewis and Allen found values of $\Delta\log k_c$ of between -0.30 and -0.40 for the 2,6-lutidine-catalyzed iodination of nitroethane.

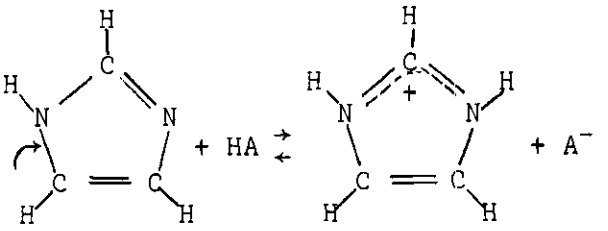
Feather and Gold (10) studied the iodination of five ketones catalyzed by several pyridine bases. With the ketones, RCH_2COR', where R is H and R' varies from CH_3 to Me_3C the values of $\Delta\log k_c$ for 2-substituted pyridines ranged from -0.12 to -0.30. For 2,6-substituted pyridines the value of $\Delta\log k_c$ ranged from -0.84 for acetone and 2,6-

lutidine to -1.38 for 2,6-lutidine and pinacolone. Of the other two ketones studied, diethyl ketone and cyclohexanone, diethyl ketone followed the pattern of the other ketones, but cyclohexanone appeared to be more hindered. In the case of 2,4,6-trimethylpyridine and cyclohexanone $\Delta \log k_c$ was -1.69. It should be noted that in the article by Feather and Gold, $\Delta \log k_c$ was defined as being equal to $\log k_c - GK_B$. This must be an error.

Westheimer and Covitz (14) studied the mutarotation of glucose and hydrolysis of methyl ethylene phosphate with several hindered pyridine bases and found large $\Delta \log k_c$ values. It is not completely clear that these were studies of simple proton removal.

An examination of the various reactions studied and the amount of hindrance in the substrate and the catalyst would seem to indicate that the hydrogen removed from isobutyraldehyde is more hindered than those removed in the other cases. The proton removed in the iodination of 2-nitropropane would appear to be almost as hindered as the one removed in isobutyraldehyde but due to the much greater acidity of the hydrogen alpha to the nitro group, the removal may occur earlier on the reaction coordinate than it does in the case of the isobutyraldehyde. This permits the methyl groups moving into coplanarity with nitrogen and the alpha carbon to be further away from the attacking base in the transition state.

Unexpectedly, N-methylimidazole has a slower rate than might be expected from its basicity. This rate deterrence might well be due to another effect--geometric change. Looking at Equation 5



(5)

it can be seen that in the case of imidazoles protonation would lengthen one carbon-nitrogen bond and shorten another so that the two become equal.

The single-bonded nitrogen substituent illustrated by the arrow in Equation 5 cannot act as effectively as an electron-donating substituent in the transition state, where the carbon-nitrogen bond is still quite long, as it can in the imidazolium ion, where the bond is shorter and overlap between the pi orbitals is more extensive.

Two amines, trimethylamine and triethylenediamine, are much better catalysts than would be expected, as is indicated on the Bronsted plot. In the case of trimethylamine the acceleration is probably due to the fact that the three methyl groups do not hinder the approach to the isobutyraldehyde-2-d molecule. Triethylenediamine accelerates the reaction more than anticipated from the pK_B because the alkyl groups are all pinned back allowing a closer approach.

In the other alkyl tertiary amines, it is difficult to say how much they are hindered. But in one group of compounds, the steric hindrance may be similar. The kinetics of the deuterium exchange of isobutyraldehyde-2-d using N-methylmorpholine, N-methylpiperidine and N-methylpyrrolidine as catalysts were followed in order to study hindrance in systems with two of the alkyl groups on nitrogen held

back in a ring. From the Bronsted plot it would appear that the six-membered ring compounds are more hindered than the N-methylpyrrolidine although the N-methylmorpholine ring may be affected by introduction of the oxygen atom. Brown and co-workers (68) have reported qualitatively similar data in the more hindered trimethylboranamine system in the gas phase. In spite of the fact that pyrrolidine is only a slightly stronger base than piperidine, the dissociation equilibrium constant for the trimethylborane-piperidine complex is ten times higher than that of the pyrrolidine complex. If the two saturated six-membered ring compounds do follow Bronsted's Law, β is 0.39.

Trimethylamine-N-oxide is definitely a better catalyst than acetate ion, but only slightly better than an unhindered pyridine of its basicity would be. The amine oxide is a relatively unhindered base whose reactivity should not be reduced by a geometric change effect. Whatever the cause the amine oxide reactivity is small enough that oxidation of small amounts of tertiary amines to amine oxides will not significantly complicate determinations of catalytic constants for tertiary amines.

Two-Component Catalyst Deuterium Exchange Kinetics

The two-catalyst system of a tertiary and a primary amine was studied to look for a termolecular term in the deuterium exchange of isobutyraldehyde-2-d. A system of N-methylmorpholine and methylammonium chloride was studied. In the exchanging solution, the methylam-

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68. Brown's work is discussed by H. C. Brown, D. H. McDaniel, and O. Häfliger in E. A. Braude and F. C. Nachod, Determination of Organic Structures by Physical Methods, Vol. 1, Academic Press Inc., New York, N. Y., 1955, Chap. 14.

monium ions might be expected to participate in the exchange in the following manner:

$$MeNH_3^+ \rightleftarrows MeNH_2 + H^+ \qquad \frac{k_w}{K_{MeNH_2}} \qquad (6)$$

$$MeNH_2 + Me_2CDCHO \rightleftarrows Me_2CDCH = NMe + H_2O \qquad K_I \qquad (7)$$

$$Me_2CDCH = NMe + H_2O \rightleftarrows Me_2CDCH = \overset{+}{N}HMe + OH^- \qquad K_{IH^-} \qquad (8)$$

$$Me_2CDCH = \overset{+}{N}HMe + NM^2 \overset{R.D.S.}{\rightleftarrows} \left| Me_2\overline{C} - CH = \overset{+}{N}HMe \leftrightarrow Me_2C = CH - NHMe \right| + D\overset{+}{N}M^2 \qquad (9)$$

Step 9 is followed by a series of rapid steps resulting in the formation of the protium form of isobutyraldehyde. In addition to this route for exchange, the removal of the deuterium directly from the aldehyde by the amine takes place. The observed rate of deuterium exchange (R) is then Equation 10 where NM^2 is the N-methylmorpholine concentration.

$$R = k\frac{K_I K_{IH^+}}{K_{MeNH_2}} + [MeNH_3^+][NM^2][IBA\text{-}2\text{-}d] + k_{NM^2}[NM^2][IBA\text{-}2\text{-}d] \qquad (10)$$

To test the feasibility of the mechanism involving the imine intermediate, several experiments were made maintaining a 0.211 M N-methylmorpholine concentration and varying the methylammonium chloride concentration. A plot of the observed first-order rate constants for

deuterium exchange versus the methylammonium chloride concentration has as the slope, from Equation 10:

$$\left(\frac{\delta \text{ Obs. Rate Con.}}{\delta[MeNH_3^+]}\right)_{NM^2} = \frac{kK_IK_{IH^+}[NM^2]}{K_{MeNH_2}}$$

Table 20 is a tabulation of the observed first-order rate constants at various methylammonium chloride concentrations and Fig. 5 is a plot of the data. The slope of the plot is 4.23×10^{-4} $sec.^{-1}$ and the intercept is 3.80×10^{-5} $sec.^{-1}$ The intercept corresponds to the first-order rate constant for deuterium exchange from isobutyraldehyde-2-d catalyzed by 0.211 M N-methylmorpholine. The slope of the plot divided by the N-methylmorpholine concentration will yield the term, $kK_IK_{IH^+}/K_{MeNH_2}$, for methylammonium chloride. The value of K_I, determined by Dr. Julien Mulders at 25°, is 90, and K_{MeNH_2} is 4.25×10^{-4} (59). The basic ionization constant for enamine, I, is not known.

As a check of this work, experiments were conducted in which the N-methylmorpholine buffer concentration was varied and the methylammonium chloride concentration remained constant. The results of these experiments are in Table 20. A plot, Fig. 6, of the observed first-order rate constants for deuterium exchange from isobutyraldehyde-2-d obtained in these experiments versus the concentration of N-methylmorpholine should have as the slope from Equation 9:

$$\left(\frac{\delta \text{ Obs. Rate Con.}}{\delta[NM^2]}\right)_{MeNH_3^+} = \frac{kK_IK_{IH^+}[MeNH_3^+]}{K_{MeNH_2}} + k_{NM2} \qquad (11)$$

Table 20. Kinetic Data on Two-Component Deuterium Exchange of Isobutyraldehyde-2-d

Experiment Number 2C-	[IBA]	$MeNH_3Cl$	B.[a] Moles/Liter	BH^+	$NaClO_4$	$k_{obs.} \times 10^4$ $sec.^{-1}$
4,9	.14	0.22	0.169	0.145	0.036	1.05
5	.14	0.22	0.127	0.109	0.073	0.813
6	.14	0.22	0.084	0.073	0.109	0.515
7	.14	0.22	0.211	0.182	0	1.37
8	.14	0.22	0.154	0.424	0	1.12
10	.14	0.22	0.106	0.091	0.091	0.675
16,26,32	.14	0.22	0.211	0.212	0	1.28
17	.14	0	0.211	0.212	0.22	0.375
18	.14	0.132	0.211	0.212	0.09	0.955
19,23,27,33	.14	0.176	0.211	0.212	0.044	1.13
20,29	.14	0.088	0.211	0.212	0.132	0.731
28	.14	0.044	0.211	0.212	0.176	0.578
21	.22	0.030	0.187	0.075	0.141	0.450
22	.22	0.070	0.187	0.075	0.105	0.588
23	.22	0.176	0.187	0.075	0	0.99
24	.22	0.141	0.189	0.073	0	0.670
25	.22	0.141	0.189	0.073	0.035	0.653
30	.14	0.22	0.167	0.168	0.042	0.933
31	.14	0.22	0.125	0.126	0.084	0.750

a. B is concentration of N-methylmorpholine.

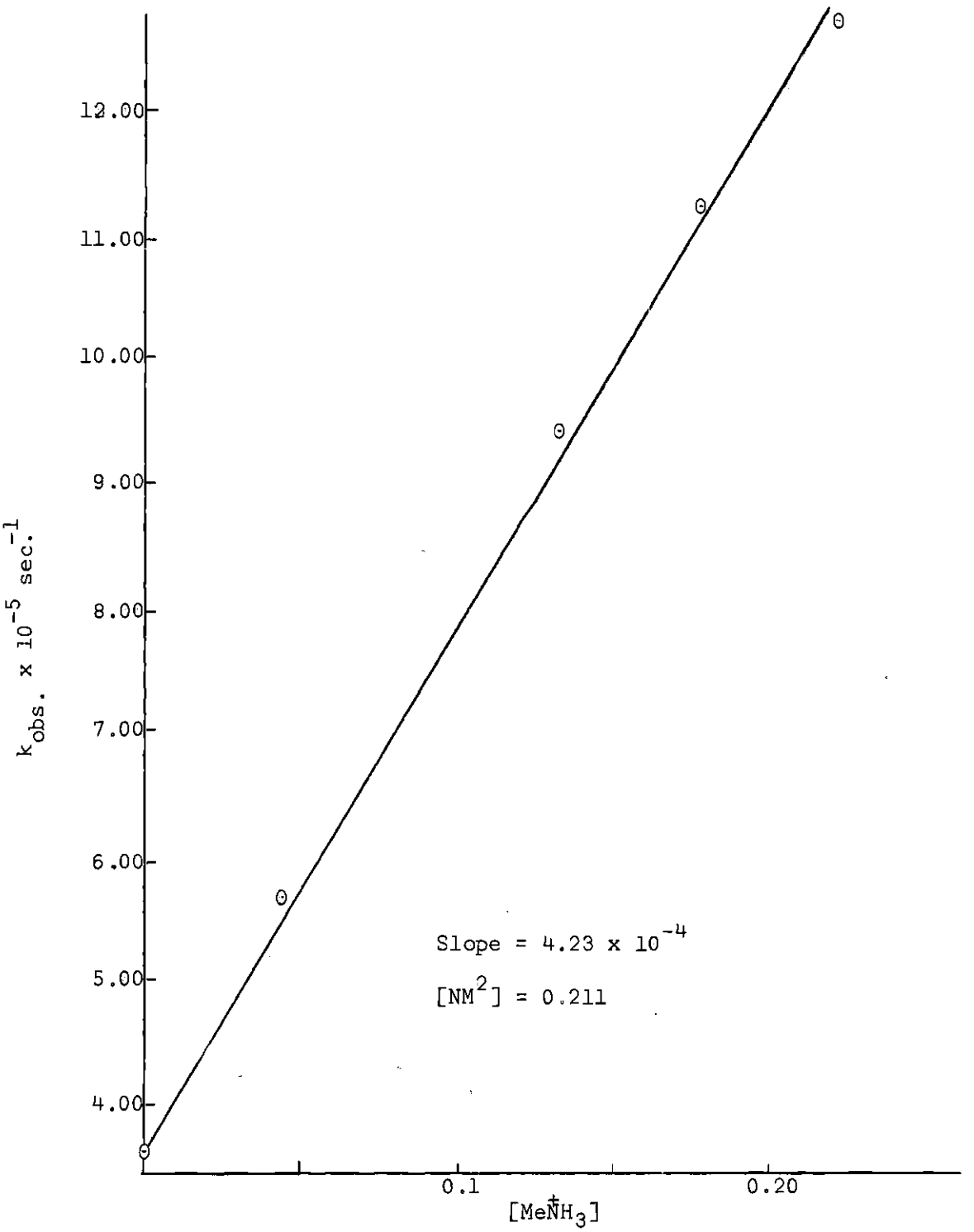

Figure 5. Plot of the Methylammonium Ion Concentration vs. the First-Order Rate Constant for Deuterium Exchange from Isobutyraldehyde-2-d at a Constant N-Methylmorpholine Concentration of 0.211 M

The value obtained for the slope from Fig. 6 is 6.25×10^{-4}. The methylammonium chloride concentration was 0.22 M in these experiments. From this concentration and values for $kK_IK_{IH^+}/K_{MeNH_2}$ and k_{NM2} obtained previously the calculated value of the slope is 6.04×10^{-4}, in good agreement with that obtained in Fig. 5.

It would appear that there is a termolecular term, but the value of the catalytic rate constant cannot be determined with accuracy because the enamine ionization constant is not known. The value of the term, kK_{IH^+}, may be calculated to be 9.4×10^{-9} if the value of K_I is assumed to be the same at 35° as at 25°.

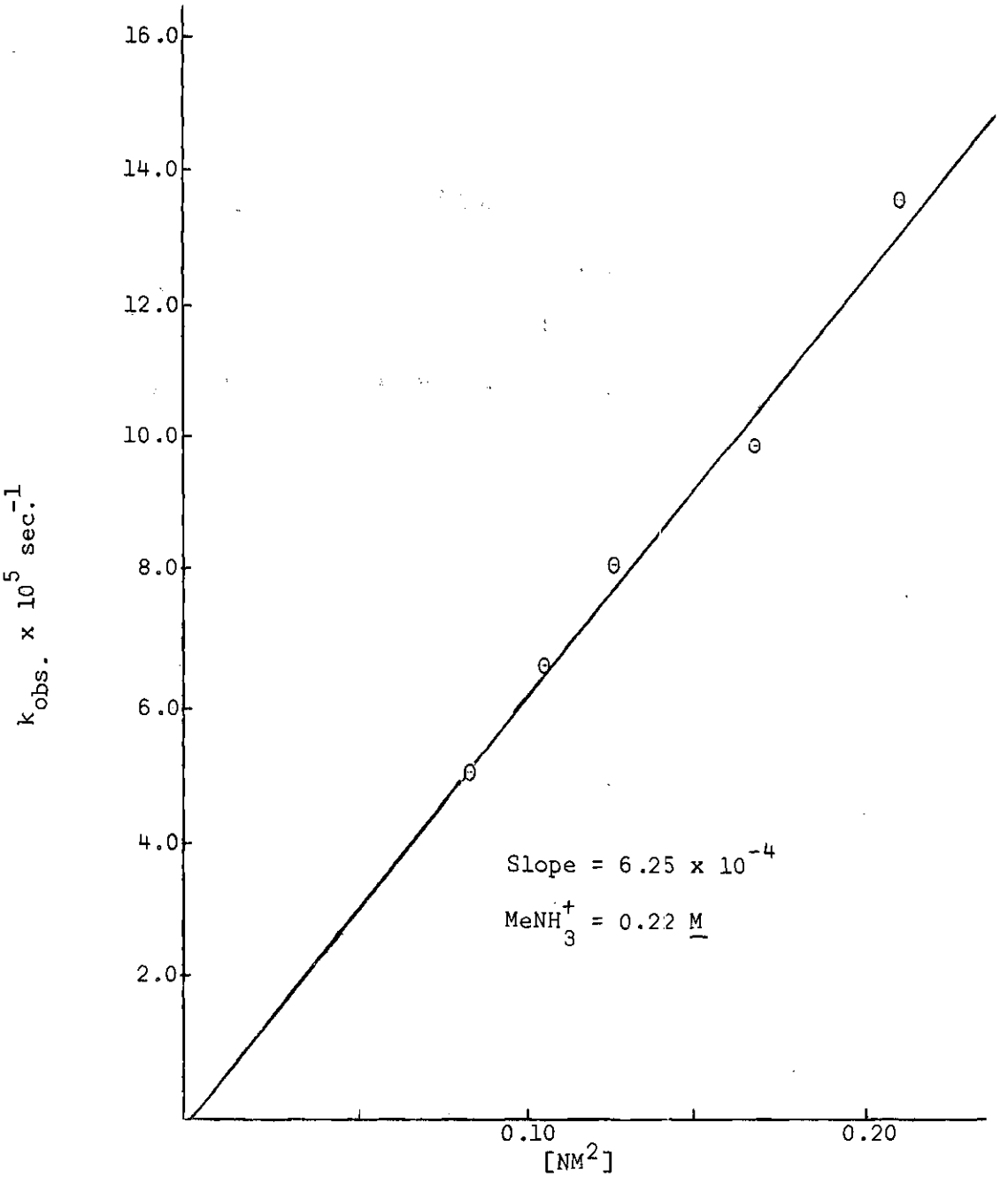

Figure 6. Plot of the N-Methylmorpholine Concentration vs. the First-Order Rate Constant for Deuterium Exchange from Isobutyraldehyde-2-d at a Constant Methylammonium Ion Concentration of 0.22 M

CHAPTER IV

CONCLUSION

The work described in this study has been done with the aim of studying the behavior of various tertiary amines and oxygen bases as catalysts for the proton removal step of a chemical reaction. The information will be used in attempting to make polyfunctional catalysts for reactions involving proton removal as one of the steps.

The most reactive catalysts for their basicity are trimethylamine and triethylenediamine. It therefore appears that tertiary aliphatic amines in which steric hindrance has been reduced to a minimum are the most effective of the catalysts we have studied. For catalysis in the pH range near neutrality the two amines mentioned have the disadvantage that they would exist largely as their conjugate acids under such conditions. Since most reactions that are catalyzed by enzymes take place in physiological media that are neutral, or approximately neutral, aqueous solutions, functional groups with basicities similar to those of typical saturated aliphatic tertiary amines have obvious deficiencies for enzyme model studies. Synthesis of unhindered tertiary amines containing substituents to reduce the basicity should lead to catalysts that are particularly effective near pH 7.

The study also revealed that proton removal may be sterically retarded. Proton removal by 2,6- and 2-substituted pyridines, triethylamine and triethanolamine occurs more slowly than would be expec-

ted from the basicity of the compounds as indicated from the Bronsted catalysis equation.

A kinetic study of the dealdolization of isobutyraldol reveals that the carbanion formed in the deuterium exchange of isobutyraldehyde-2-d reacts with a proton rather than with another isobutyraldehyde molecule under the conditions used in this study. This insures that the exchange being followed is actually the protonation of the carbanion formed by removal of deuterium from isobutyraldehyde-2-d.

The kinetic equation for the exchange in the presence of a two-component catalyst consisting of N-methylmorpholine--N-methylmorpholinium perchlorate and methylammonium chloride has two terms, one first order in N-methylmorpholine and in methylammonium ion. The second order term indicates that the small amount of methylamine present reacts with the isobutyraldehyde-2-d to form an imine that exchanges rapidly when catalyzed by N-methylmorpholine.

APPENDIX

Table 21. Summary of Deuterium Exchange Kinetics Data

Catalysts	Concentration B	Concentration BH	k_{ob} $sec.^{-1}$	k_{cor} $sec.^{-1}$
Sodium p-cresolate	0.0275	0.0527	8.03×10^{-5}	$7.72\ x^{c}\ 10^{-5}$
Sodium o-cresolate	0.0243	0.0210	5.45×10^{-5}	$5.24\ x^{c}\ 10^{-5}$
Sodium phenoxide	0.0267	0.0371	4.61×10^{-5}	$4.37\ x^{c}\ 10^{-5}$
Sodium phenoxide	0.0299	0.0339	5.25×10^{-5}	$4.96\ x^{c}\ 10^{-5}$
Sodium p-chlorophenoxide	0.0407	0.0627	5.13×10^{-5}	$5.07\ x^{c}\ 10^{-5}$
Sodium m-chlorophenoxide	0.0275	0.0393	1.90×10^{-5}	$1.87\ x^{c}\ 10^{-5}$
Sodium o-chlorophenoxide	0.0244	0.0620	8.18×10^{-6}	8.18×10^{-6}
Sodium m-nitrophenoxide	0.0143	0.0340	4.08×10^{-6}	$4.04\ x^{c}\ 10^{-6}$
Sodium p-nitrophenoxide	0.0295	0.0363	1.53×10^{-6}	$1.51\ x^{b}\ 10^{-6}$
Trimethylamine-N-oxide	0.332	0.078	1.75×10^{-6}	$1.73\ x^{b}\ 10^{-4}$
Sodium acetate	0.833	0.156	7.40×10^{-7}	$7.22\ x^{b}\ 10^{-7}$
Sodium acetate	0.319	0.319	3.00×10^{-7}	$2.82\ x^{b}\ 10^{-7}$
Sodium hydroxide	0.00369		8.51×10^{-5}	8.51×10^{-5}
Sodium hydroxide	0.00855		2.43×10^{-4}	2.43×10^{-4}
Sodium hydroxide	0.0192		5.61×10^{-4}	5.61×10^{-4}
Perchloric acid		0.565[d]	1.78×10^{-5}	1.78×10^{-5}

b. Corrected for water catalysis.

c. Corrected for hydroxide ion catalysis.

d. Acid concentration.

Table 22. Summary of Deuterium Exchange Kinetics Data

Catalysts	Concentration B	Concentration BH^+	$k_{ob.}$ sec.$^{-1}$	$k_{cor.}$ sec.$^{-1}$	
Trimethylamine	0.0312	0.0392	5.00×10^{-4}	5.00×10^{-4}	
Trimethylamine	0.0125	0.0227	2.03×10^{-4}	2.03×10^{-4}	
Trimethylamine	0.0218	0.0309	3.45×10^{-4}	3.45×10^{-4}	
Trimethylamine	0.0080	0.0270	1.44×10^{-4}	1.44×10^{-4}	
N-Methylpyrrolidine	0.0148	0.0279	1.18×10^{-4}	1.13×10^{-4}	c
N-Methyldiethylamine	0.0187	0.0556	1.38×10^{-4}	1.36×10^{-4}	c
Triethylenediamine	0.0250	0.0215	1.62×10^{-4}	1.62×10^{-4}	
D-Methylpiperidine	0.0154	0.0157	2.63×10^{-5}	2.24×10^{-5}	c
N,N,N′,N′-Tetramethyl-ethylenediamine	0.0323	0.0556	4.48×10^{-5}	4.48×10^{-5}	
β-Dimethylaminoethanol	0.0281	0.0350	2.73×10^{-5}	2.65×10^{-5}	c
Triethylamine	0.0136	0.040	1.56×10^{-5}	1.05×10^{-5}	c
N-Methylmorpholine	0.0246	0.0375	4.51×10^{-6}	4.51×10^{-6}	
N-Methylimidazole	0.0471	0.1232	7.13×10^{-7} b	6.95×10^{-7}	b
N-Methylimidazole	0.1454	0.3408	2.47×10^{-6}	2.47×10^{-6}	
Triethanolamine	0.237	0.142	9.17×10^{-7}	8.59×10^{-7}	a,b,c
3,4-Lutidine	0.127	0.112	4.05×10^{-6}	4.05×10^{-6}	
4-Picoline	0.1788	0.341	3.00×10^{-6}	3.00×10^{-6}	
4-Picoline	0.0556	0.1232	8.0×10^{-7}	7.82×10^{-7}	b
2,4-Lutidine	0.170	0.005	1.85×10^{-6}	1.81×10^{-6}	c
Pyridine	0.714	0.215	5.63×10^{-6}	5.63×10^{-6}	
2,4,6-Trimethylpyridine	0.0891	0.1512	1.10×10^{-7}	6.5×10^{-8}	a,b,c
2,6-Dimethylpyridine	0.161	0.345	8.55×10^{-8}	4.45×10^{-8}	a,b,c

a. Corrected for isobutyrate ion catalysis.

b. Corrected for water catalysis.

c. Corrected for hydroxide ion catalysis.

Table 23. Per Cent Deuterium Correction Curve Data

Per Cent D	H_1	D_2	D_2/D_2+H_1
10	17.56	3.71	0.174
14	18.38	3.53	0.161
20	15.12	5.50	0.267
30	14.69	7.21	0.329
34	14.89	8.42	0.361
40	11.85	8.50	0.418
44	12.19	10.40	0.460
50	10.36	10.80	0.510
54	12.43	13.43	0.519
60	7.33	10.40	0.587
64	9.62	13.83	0.590
70	7.50	13.45	0.642
74	7.42	16.38	0.688
80	6.47	17.55	0.731
84	5.76	17.12	0.748
90	5.46	23.69	0.813
94	3.17	17.65	0.848

Table 24. Hydroxide Ion Catalyzed Deuterium Exchange--0.00369 M

0.00369 M NaOH 0.0109 M Isobutyrate Ion 0.21 M Isobutyraldehyde

Time Minutes	D_1	H_2	Per Cent D
0			
5.5	17.5	4.2	91
9.0	17.0	5.0	84
23.0	16.2	6.4	80
48.0	13.5	6.8	74
77.0	10.8	7.8	64
156.0	8.5	11.2	73

$k_{ob} = 8.51 \times 10^{-5}$ sec.$^{-1}$

Table 25. Hydroxide Ion-Catalyzed Deuterium Exchange--0.00855 M

0.00855 M NaOH 0.0109 M Isobutyrate Ion 0.21 M Isobutyraldehyde

Time	D_2	D_1	Per Cent D
1.0	17.4	2.3	100
18.5	14.3	5.7	84
30.5	12.8	7.5	76
45.5	8.1	8.7	49
60.5	6.5	8.7	42
75.8	5.4	9.7	33

$k_{ob} = 2.43 \times 10^{-4}$ sec.$^{-1}$

Table 26. Hydroxide Ion-Catalyzed Deuterium Exchange--0.0192 M

0.0192 M NaOH 0.0149 M Isobutyrate Ion 0.21 M Isobutyraldehyde

Time	D_2	H_1	Per Cent D
1.0	21.8	4.0	97.0
2.5	22.9	5.8	89.5
5.7	18.8	6.8	81.3
10.8	17.8	10.3	68.0
12.8	15.3	10.5	62.8
17.8	13.4	11.6	56.1
21.1	12.8	13.9	48.5
24.3	11.8	14.2	45.2
28.0	11.9	16.4	41.0

$k_{ob} = 5.61 \times 10^{-4}$ sec.$^{-1}$

Table 27. Hydrogen Ion-Catalyzed Deuterium Exchange

0.565 M $HClO_4$ 0.320 M Isobutyraldehyde

Time Minutes	D_2	H_1	Per Cent D
10	22.2	2.7	99
24	22.2	3.1	98.5
58	20.5	3.7	95.5
94	19.6	4.3	92.0
125	19.6	5.4	87.5
148	18.6	5.6	85.5
187	27.0	8.2	81.5
273	21.5	10.4	73.0
381	19.2	12.1	65.5
513	20.9	17.7	56.0
518	22.0	17.2	58.5
626	17.1	19.3	47.0
847	15.0	22.0	39.0
1033	17.5	23.2	37.0

$k_{obs.} = 1.78 \times 10^{-5}$ sec.$^{-1}$

Table 28. Base-Catalyzed Dealdolization of Isobutyraldol

0.039 M Triethylenediamine 0.0424 M Isobutyraldol
0.0074 M Triethylenediamine monohydroperchlorate 0.0006 M Total Acid
2.52×10^{-5} M Hydroxide Ion

Time Seconds	Aldehyde V_B	Aldehyde ξ_B	Aldehyde B	Aldol V_A	Aldol ξ_A	Aldol A
1800	4.60	0.88	4.05	11.86	1.05	12.26
2400	5.20	1.00	5.20	10.90	1.15	12.54
3000	5.60	0.95	5.32	9.15	1.20	10.98
3660	5.55	1.00	5.55	8.10	1.15	9.32
4260	6.10	1.05	6.41	6.60	1.45	9.57
4800	8.30	1.00	8.30	8.40	1.20	10.08
5400	9.78	0.90	8.80	7.70	1.20	9.24
6000	10.72	0.90	9.65	7.30	1.15	8.40
7240	10.70	0.95	10.17	6.05	1.10	6.66

Table 29. Base-Catalyzed Dealdolization of Isobutyraldol

0.0229 M Triethylenediamine
0.0158 M Triethylenediamine monohydroperchlorate
0.0530 M Isobutyraldol
0.00104 M Total Acid
6.80×10^{-6} M Hydroxide Ion

Time Seconds	Aldehyde V_B	ξ_B	B	Aldol V_A	ξ_A	A
4110	2.92	0.60	1.752	12.80	1.05	13.44
5200	4.00	0.85	3.40	12.60	1.40	17.64
5460	4.70	0.70	3.29	14.70	0.95	13.97
7740	8.50	0.50	4.25	16.80	0.65	10.92
9720	8.60	0.58	4.99	15.90	0.73	11.61
11520	9.45	0.65	6.14	13.60	0.76	10.34
13440	10.50	0.62	6.51	12.50	0.76	9.50
14610	10.60	0.75	7.95	11.50	1.00	11.50

Table 30. Base-Catalyzed Dealdolization of Isobutyraldol

0.0086 M Trimethylamine
0.0070 M Trimethylammonium Ion
0.0530 M Isobutyraldol
0.00104 M Total Acid
4.10×10^{-4} M Hydroxide Ion

Time Seconds	Aldehyde Peak V_B	ξ_B	B	Aldol Peak V_A	ξ_A	A
570	3.60	0.68	2.45	15.20	0.95	14.40
955	5.65	0.70	3.96	12.00	0.95	11.40
1320	6.95	0.90	6.26	10.30	1.10	11.33
2240	14.40	0.65	9.36	10.05	0.70	7.04
2610	13.80	0.70	9.66	9.30	0.72	6.70
2990	14.00	0.65	9.10	7.40	0.80	5.92
3562	15.15	0.65	9.85	6.38	0.65	4.15

Table 31. Triethylamine-Catalyzed Deuterium Exchange

0.0136 M Amine
0.21 M Isobutyraldehyde
0.040 M Ammonium Ion
0.0052 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
1.0	20.6	.04	100
9.0	22.6	1.04	61.5
11.1	9.8	9.59	51.0
13.5	9.6	10.68	47.2

$k_{ob} = 1.56 \times 10^{-5} sec.^{-1}$

Table 32. Trimethylamine-Catalyzed Deuterium Exchange--0.0312 M

0.0312 M Amine
0.0392 M Ammonium Ion
0.21 M Isobutyraldehyde-2-d
0.0064 M Isobutyrate Ion

Time Seconds	D_2	H_1	Per Cent D
0	21.4	3.5	97.0
218	11.0	3.3	86.2
495	10.1	4.5	77.2
765	13.7	9.45	65.3
1028	13.6	10.2	62.6
1363	10.6	11.8	50.5
1800	10.9	12.9	49.0
2254	8.4	16.0	34.5
2395	7.5	16.2	31.0

$k_{obs.} = 5.00 \times 10^{-4} sec.^{-4}$

Table 33. Trimethylamine-Catalyzed Deuterium Exchange--0.0125 M

0.0125 M Amine
0.0227 M Ammonium Ion
0.21 M Isobutyraldehyde-2-d
0.0064 M Isobutyrate Ion

Time Seconds	D_2	H_1	Per Cent D
0	20.85	2.80	99.5
235	14.70	2.80	94.6
594	17.40	5.00	84.9
1855	13.20	8.20	68.5
2827	11.70	10.7	56.5
4044	9.50	12.9	44.5
5312	7.90	15.5	33.7
7250	6.70	18.4	25.2

$k_{obs.} = 2.03 \times 10^{-4}$ sec.$^{-1}$

Table 34. Trimethylamine-Catalyzed Deuterium Exchange--0.218 M

0.0218 M Amine
0.0309 M Ammonium Ion
0.21 M Isobutyraldehyde-2-d
0.0064 M Isobutyrate Ion

Time Seconds	D_2	H_1	Per Cent D
0	20.3	3.05	98.0
204	17.2	5.1	86.5
892	12.5	7.9	67.7
1997	9.1	10.4	49.8
2968	8.6	16.4	34.8
5190	5.8	19.6	20.3

$k_{obs.} = 3.45 \times 10^{-4}$ sec.$^{-1}$

Table 35. Trimethylamine-Catalyzed Deuterium Exchange--0.0080 M

0.0080 M Amine
0.0270 M Ammonium Ion
0.21 M Isobutyraldehyde-2-d
0.0089 M Isobutyrate Ion

Time Seconds	D_2	H_1	Per Cent D
0	18.40	3.9	92.7
387	14.55	3.50	90.6
855	16.4	4.65	87.5
1940	14.90	6.20	78.8
2839	12.8	7.70	69.2
3755	12.3	10.20	59.1
4702	11.5	12.10	52.2
5508	9.3	12.40	45.0
6105	9.9	14.20	42.7

$k_{obs.} = 1.44 \times 10^{-4}$ sec.$^{-1}$

Table 36. N-Methylmorpholine-Catalyzed Deuterium Exchange

0.0246 M Amine
0.32 M Isobutyraldehyde
0.0375 M Ammonium
0.0150 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
23	20.8	3.00	99.0
68	20.0	2.90	98.9
292	19.2	3.82	94.0
394	23.0	4.92	92.5
548	21.5	5.40	89.5
1436	16.0	8.72	70.0
3266	14.0	14.50	50.0

$k_{obs.} = 4.51 \times 10^{-6}$ sec.$^{-1}$

Table 37. Triethylenediamine-Catalyzed Deuterium Exchange

0.0250 M Amine
0.0215 M Ammonium Ion
0.21 M Isobutyraldehyde
0.0150 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
4	23.3	3.9	97.0
10	22.2	5.1	95.2
16	21.7	6.4	86.0
22	20.5	7.4	81.2
29	19.3	8.7	75.2
46	16.4	11.2	63.0
69	13.6	13.6	51.6
90	10.8	16.1	39.0
125	8.4	17.1	29.0

$k_{obs.} = 1.62 \times 10^{-4}$ sec.$^{-1}$

Table 38. β-Dimethylaminoethanol-Catalyzed Deuterium Exchange

0.0281 M Amine
0.0350 M Ammonium Ion
0.21 M Isobutyraldehyde
0.0052 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
18	19.0	0.05	
94	19.8	4.5	87.5
143	22.4	6.9	82.0
195	21.8	9.5	75.0
231	20.0	11.3	68.5
284	22.0	14.8	64.0
330	20.6	16.7	59.0
406	18.8	17.4	51.0
471	16.7	19.4	49.0
543	14.5	20.8	43.0

$k_{obs.} = 2.73 \times 10^{-5}$ sec.$^{-1}$

Table 39. N-Methyldiethylamine-Catalyzed Deuterium Exchange

0.0187 M Amine
0.0556 M Ammonium Ion
0.30 M Isobutyraldehyde
0.010 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
25	16.75	4.75	82.5
44	17.85	9.2	67.0
11	19.0	3.0	91.0
60	16.2	11.3	62.5
79	14.8	15.0	52.0
94	14.4	15.5	46.5
113	12.2	19.7	37.0
132	11.3	21.6	33.5
150	9.2	21.6	30.0

$k_{obs.} = 1.38 \times 10^{-4}$ sec.$^{-1}$

Table 40. N,N,N',N'-Tetramethylethylenediamine-Catalyzed Deuterium Exchange

0.0323 M Amine
0.0556 M Ammonium Ion
0.30 M Isobutyraldehyde
0.010 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
11	19.2	2.10	95
37.5	17.2	3.40	87.5
62	16.4	4.90	80.3
97.5	14.2	6.10	72.8
127	16.4	8.40	68.5
179	15.0	11.00	59.3
206	13.2	11.20	55.5
242	12.1	11.90	51.5

$k_{obd.} = 4.48 \times 10^{-5}$ sec.$^{-1}$

Table 41. N-Methylimidazole-Catalyzed Deuterium Exchange--0.0471 M

0.0471 M Amine
0.1232 M Ammonium Ion
0.30 M Isobutyraldehyde
0.0158 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
.50	19.8	1.1	100
1.3	17.4	1.3	97.5
11.7	23.4	2.1	96.5
25.0	23.7	3.5	91.0
40.2	20.9	4.0	87.6
63.5	20.3	5.6	82.0
87.3	22.6	7.8	77.5
109.8	20.8	8.4	74.0
141.5	21.6	10.2	70.5
164.5	20.8	11.5	67.0

$k_{obs.} = 7.13 \times 10^{-7}$ sec.$^{-1}$

Table 42. N-Methylimidazole-Catalyzed Deuterium Exchange--0.1454 M

0.1454 M Amine
0.3408 M Ammonium Ion
0.52 M Isobutyraldehyde
0.0193 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
0.7	22.9	1.20	99
6.8	19.6	2.35	93
11.8	22.7	4.10	89
22.0	22.1	6.30	81
31.0	18.2	7.00	75
45.5	20.1	11.85	65
58.0	22.9	16.95	60
72.0	22.7	22.10	52
82.5	18.6	20.30	49
100.0	15.7	22.30	42

$k_{obs.} = 2.47 \times 10^{-6}$ sec.$^{-1}$

Table 43. Triethanolamine-Catalyzed Deuterium Exchange

0.237 M Amine
0.142 M Ammonium Ion
0.55 M Isobutyraldehyde
0.0080 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
7.5	20.0	2.6	92.5
17.0	20.6	3.3	90.5
24.8	19.6	3.4	89.0
34.0	20.5	4.2	85.0
34.0	19.9	3.8	87.0
153.3	22.1	16.1	60.0
251.5	13.0	18.0	41.0

$k_{obs.} = 9.17 \times 10^{-7}$ sec.$^{-1}$

Table 44. Acetate Ion-Catalyzed Deuterium Exchange--0.833 M

0.833 M Acetate Ion
0.156 M Acetic Acid
0.52 M Isobutyraldehyde
0.0193 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
1	20.45	1.2	99
7	21.7	1.4	96.5
12	22.5	1.6	95.5
22	21.7	2.5	94.3
31	24.2	3.5	91.3
45.5	23.0	3.7	90.0
58	19.6	3.9	87.7
72	21.0	4.8	85.0
82.5	24.5	7.2	80.5
100	23.5	8.1	77.5
324.5	12.5	17.2	42.5

$k_{obs.} = 7.40 \times 10^{-7}$ sec.$^{-1}$

Table 45. Acetate Ion-Catalyzed Deuterium Exchange--0.319 M

0.319 M Acetate Ion
0.319 M Acetic Acid
0.16 M Isobutyraldehyde

Time (Hours)	D_2	H_1	Per Cent D
0	21.5	2.9	100
108	19.0	3.7	94
281	18.7	8.5	75
440	15.0	9.8	64
440	13.1	8.5	64
611	10.6	10.6	51

$k_{obs.} = 3.00 \times 10^{-7}$ sec^{-1}

Table 46. 2,4-Lutidine-Catalyzed Deuterium Exchange

0.170 M Amine
0.21 M Isobutyraldehyde-2-d
0.005 M Ammonium Ion
0.005 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
0	21.4	.03	100
0	24.8	2.4	97.5
23.7	22.0	5.7	85.5
50.41	18.2	9.2	72.0
72.95	15.0	9.4	61.0
99.02	17.4	18.0	52.5

$k_{obs.} = 1.85 \times 10^{-6}$ sec^{-1}

Table 47. 4-Picoline-Catalyzed Deuterium Exchange--0.0556 M

0.0556 M Amine
0.1232 M Ammonium Ion
0.30 M Isobutyraldehyde-2-d
0.0105 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
0	22.8	1.30	99
0.7	21.4	1.10	99
16.5	20.9	4.55	95
30.5	23.3	3.30	91.5
45.0	20.9	4.55	86.0
68.5	19.2	6.10	79.0
92.5	22.9	9.10	74.5
115.5	21.1	10.80	68.5
146.8	22.4	13.80	64.0
170.0	20.4	14.00	61.0
188.0	13.6	9.50	61.0
261.0	16.6	13.80	56.0
282.0	14.8	16.70	48.0

$k_{obs.} = 8.0 \times 10^{-7}$ sec.$^{-1}$

Table 48. 4-Picoline-Catalyzed Deuterium Exchange--0.1788 M

0.1788 M Amine
0.341 M Ammonium Ion
0.52 M Isobutyraldehyde-2-d
0.0193 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
.5	22.5	0.9	99.0
6.5	21.3	2.6	93.3
11.8	23.3	4.8	87.0
23.0	20.6	7.1	77.5
31.0	21.3	9.8	71.3
45.3	23.6	18.2	58.3
58.0	20.7	19.5	53.0
72.0	17.0	21.0	45.5
82.0	13.9	20.0	41.0
100.0	10.0	20.3	33.0

$k_{obs.} = 3.00 \times 10^{-6}$ sec.$^{-1}$

Table 49. 2,4,6-Trimethylpyridine-Catalyzed Deuterium Exchange

0.0891 M Amine
0.1512 M Ammonium Ion
0.52 M Isobutyraldehyde-2-d
0.022 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
1	22.8	1.1	100
210	21.8	3.1	93 (Twice)
534	20.1	6.1	80 (Twice)

$k_{obs.} = 1.10 \times 10^{-7}$ sec.$^{-1}$

Table 50. 2,6-Lutidine-Catalyzed Deuterium Exchange

0.161 M Amine
0.345 M Ammonium Ion
0.52 M Isobutyraldehyde-2-d
0.022 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
1	21.6	1.1	100
210	21.1	2.4	94.5 (Twice)
534	20.1	4.7	85 (Twice)

$k_{obs.} = 8.55 \times 10^{-8}$ sec.$^{-1}$

Table 51. Pyridine-Catalyzed Deuterium Exchange

0.714 M Amine
0.215 M Ammonium Ion
0.55 M Isobutyraldehyde-2-d
0.008 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
120	22.7	2.7	93
456	19.8	5.0	83
622	23.4	8.3	77
736	21.8	6.8	81
1017	20.5	10.4	69
1017	21.7	10.9	69
1292	23.6	15.5	63
1292	23.4	15.0	63
1475	20.1	15.6	58
1591	20.9	16.9	57
1593	20.2	16.5	57
2037	18.8	17.8	52
2040	18.0	18.0	51
2332	18.8	23.3	46
2334	18.4	23.4	45

$k_{obs.} = 5.63 \times 10^{-6}$ sec.$^{-1}$

Table 52. 3,4-Lutidine-Catalyzed Deuterium Exchange

0.127 M Amine
0.112 M Ammonium
0.55 M Isobutyraldehyde-2-d
0.008 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
103	22.9	2.8	93
463	22.5	3.7	90
625	19.9	4.6	85
740	20.8	4.8	85
1024	23.7	8.3	77
1298	18.6	8.8	71
1298	19.8	8.4	73
1485	19.7	9.5	70
1486	18.5	8.9	70
1597	18.6	9.2	70
1599	18.3	10.7	66
2045	21.9	15.9	60
2045	22.3	16.3	59
2337	22.1	18.0	57
2339	24.2	19.2	58

$k_{obs.} = 4.05 \times 10^{-6}$ sec.$^{-1}$

Table 53. Trimethylamine-N-Oxide-Catalyzed Deuterium Exchange

0.332 M Amine-N-Oxide
0.078 M Ammonium-N-Oxide
0.55 M Isobutyraldehyde-2-d
0.0101 M Isobutyrate Ion

Time (Hours)	D_2	H_1	Per Cent D
0.0	24.2	1.0	100
0.75	23.0	1.1	100
2.00	24.1	1.4	99
12.0	23.7	3.6	91
25.0	19.2	4.3	86
35.5	19.8	6.5	79
48.8	20.2	9.0	74

$k_{obs.} = 1.75 \times 10^{-6}$ sec.$^{-1}$

Table 54. Sodium Phenoxide-Catalyzed Deuterium Exchange--0.0267 M

0.0267 M Phenoxide Ion
0.0371 M Phenol
0.21 M Isobutyraldehyde-2-d
0.0052 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
9	22.4	1.4	100
38	20.3	3.5	86.5
95	16.4	6.5	77.0
166	16.0	11.7	62.0
212	17.7	17.0	54.0
252	17.0	19.3	50.0
286	15.4	19.6	47.0
327	13.6	20.8	42.0
451	11.4	22.4	35.0
451	9.0	19.3	33.0

$k_{obd.} = 4.61 \times 10^{-5}$ sec.$^{-1}$

Table 55. Sodium Phenoxide-Catalyzed Deuterium Exchange--0.0299 M

0.0299 M Phenoxide
0.0339 M Phenol
0.21 M Isobutyraldehyde-2-d
0.0120 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
22	21.0	2.8	92
48	23.3	5.6	84
72	22.0	7.1	79
120	22.6	12.4	67
165	16.7	12.6	59
190	18.5	16.4	55
213	17.2	17.5	51
235	16.5	17.6	49
270	15.3	20.0	44

$k_{obs.} = 5.25 \times 10^{-5}$ sec.$^{-1}$

Table 56. Sodium m-Chlorophenoxide-Catalyzed Deuterium Exchange

0.0275 M Phenoxide Ion
0.0393 M Phenol
0.21 M Isobutyraldehyde-2-d
0.012 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
7	23.0	0.90	100
19	22.5	1.60	98
50	24.3	2.75	94
90	21.1	3.95	88
150	21.2	5.60	83
206	21.0	7.10	78
246	20.5	8.15	74
316	23.3	11.50	70
386	20.8	12.90	64
476	19.2	13.20	61
512	22.0	18.00	57
589	17.1	17.10	51

$k_{obs.} = 1.90 \times 10^{-5}$ sec.$^{-1}$

Table 57. Sodium p-Chlorophenoxide-Catalyzed Deuterium Exchange

0.0407 M Phenoxide Ion
0.0627 M Phenol
0.21 M Isobutyraldehyde-2-d
0.0012 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
11	18.3	1.72	96
56	19.3	5.00	83
84	17.8	6.60	76
116	15.8	8.40	68
168	16.8	12.70	59
204	14.4	11.80	57
236	16.3	18.75	48
282	14.5	20.40	43
352	11.7	21.35	35
425	9.6	22.80	27

$k_{obs.} = 5.13 \times 10^{-5}$ sec.$^{-1}$

Table 58. Sodium o-Chlorophenoxide-Catalyzed Deuterium Exchange

0.0244 M Phenoxide Ion
0.0620 M Phenol
0.42 M Isobutyraldehyde-2-d
0.015 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
56	22.2	2.2	95
275	22.0	5.5	84
275	22.4	5.8	83
616	21.6	9.3	73
787	20.1	11.7	66
1440	18.8	20.9	48

$k_{obs.} = 8.18 \times 10^{-6}$ sec.$^{-1}$

Table 59. Sodium o-Cresolate-Catalyzed Deuterium Exchange

0.0243 M Phenoxide
0.0210 M Phenol
0.42 M Isobutyraldehyde-2-d
0.015 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
36	20.9	3.9	89
45	17.9	4.0	85
64	16.9	5.3	79
78	21.3	8.6	74
80	20.8	8.1	75
95	20.4	9.3	71
137	18.7	11.6	65
200	17.8	15.3	55

$k_{obs.} = 5.45 \times 10^{-5}$ sec.$^{-1}$

Table 60. Sodium p-Cresolate-Catalyzed Deuterium Exchange

0.0275 M Phenoxide Ion
0.0527 M Phenol
0.21 M Isobutyraldehyde-2-d
0.0120 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
9	19.00	2.10	94
42	16.10	5.00	80
99	15.60	11.20	60
131	13.90	13.20	55
163	11.90	15.10	45
199	12.30	20.80	37
246	10.35	21.70	32
317	8.85	23.20	27

$k_{obs.} = 8.03 \times 10^{-5}$ sec.$^{-1}$

Table 61. Sodium m-Nitrophenoxide-Catalyzed Deuterium Exchange

0.0143 M Phenoxide Ion
0.0340 M Phenol
0.21 M Isobutyraldehyde-2-d
0.012 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
15	20.80	0.50	100
74	22.60	2.10	96
351	17.40	3.20	89
623	20.80	5.32	83
1168	23.25	9.50	74
1500	21.60	11.10	69
2185	23.00	14.50	63
2500	19.30	16.05	56
	17.60	16.10	54

$k_{obs.} = 4.08 \times 10^{-6}$ sec.$^{-1}$

Table 62. Sodium p-Nitrophenoxide-Catalyzed Deuterium Exchange

0.0295 M Phenoxide Ion
0.0368 M Phenol
0.28 M Isobutyraldehyde-2-d
0.010 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
427	22.8	3.7	90
3560	21.5	11.9	67
6360	15.4	13.7	54
10200	13.0	18.8	42

$k_{obs.} = 1.53 \times 10^{-6}$ sec.$^{-1}$

Table 63. N-Methylpiperidine-Catalyzed Deuterium Exchange

0.0154 M Amine
0.0157 M Ammonium Ion
0.42 M Isobutyraldehyde-2-d
0.0037 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
8	21.80	2.1	95
33	19.25	2.7	92
36	20.90	2.8	92
54	20.00	3.5	89
73	19.20	4.1	86
124	22.70	7.6	78
235	19.30	9.9	70
680	19.25	19.6	50

$k_{obs.} = 2.63 \times 10^{-5}$ sec.$^{-1}$

Table 64. N-Methylpyrrolidine-Catalyzed Deuterium Exchange

0.0148 M Amine
0.0279 M Ammonium Ion
0.42 M Isobutyraldehyde-2-d
0.0037 M Isobutyrate Ion

Time (Minutes)	D_2	H_1	Per Cent D
10.5	19.75	2.1	94
25.7	23.2	6.3	82
36.5	21.5	8.2	75.3
54.25	18.6	10.6	66
74.7	16.8	12.5	59
83.5	16.0	13.6	55.5
97	15.0	14.7	51.5
148	13.4	21.3	39

$k_{obs.} = 1.18 \times 10^{-4}$ sec.$^{-1}$

Table 65. Deuterium Exchange of Isobutyraldehyde-2-d at 60°

0.0048 M Acetate Ion
0.0025 M Isobutyric Acid

0.278 M Isobutyraldehyde-2-d

Sealed Tube Number	Time (Hours)	D_2	H_1	Per Cent D
1	0	22.9	0.90	100
2	0	23.9	1.90	100
3	0	23.8	1.50	100
1	26	24.0	2.90	93.2
2	26	19.20	2.30	93.3
3	26	23.95	2.60	94.2
1	50-1/2	23.70	3.30	91.7
2	50-1/2	19.45	2.30	93.4
3	50-1/2	23.90	3.10	92.5
1	93	21.70	3.40	90.4
2	93	22.2	3.70	89.6
3	93	23.90	3.10	92.5
1	139-1/2	23.70	5.10	86.0
2	139-1/2	18.85	4.32	85.0
3	139-1/2	20.20	4.80	84.5
1	191-1/2	21.30	5.30	84.0
2	191-1/2	21.80	5.25	84.0
3	191-1/2	21.80	5.55	84.5
1	208-3/4	22.60	6.40	81.1
2	208-3/4	23.25	7.00	80.1
3	208-3/4	20.55	5.75	80.2
1	217-1/4	23.00	6.50	81.0
2	217-1/4	23.20	7.10	79.7
3	217-1/4	23.30	7.00	80.2
1	500	21.6	14.2	62.0
2	500	23.2	14.2	64.0
3	500	19.8	13.2	62.0

Table 66. Deuterium Exchange of Isobutyraldehyde-2-d at 100°

0.00483 M Acetate Ion 0.278 M Isobutyraldehyde-2-d

0.035 M Isobutyric Acid

Sealed Tube Number	Time (Minutes)	D_2	H_1	Per Cent D
1	293	21.45	3.70	89.1
2	283	20.70	3.20	88.6
1	604	21.30	8.70	74.1
2	594	22.20	9.10	73.8
1	895	24.30	11.28	71.0
2	885	19.70	9.80	72.0
1	1141	21.55	13.40	63.6
2	1131	19.15	12.30	63.0
1	1388	20.90	15.10	59.8
2	1378	17.40	13.70	57.6
1	1984	20.72	24.60	46.0
2	1984	18.10	22.15	46.3

Table 67. Deuterium Exchange in 0.211 M N-Methylmorpholine--0.22 M Methylammonium Ion

0.211 M N-Methylmorpholine 0.22 M $MeNH_3Cl$
0.212 M N-Methylmorpholinium Ion

Experiment Number	Time (Minutes)	D_2	H_1	Per Cent D
16	15	20.1	3.6	88
16-32	17	19.3	3.7	88
16	22	19.1	4.5	85
16	27	19.4	4.9	83
32	28	16.0	5.9	76
16	29	17.9	5.5	80
32	34	16.4	6.2	76
16	35	16.8	6.3	76
26	36	14.6	5.8	74
16	38	15.9	6.7	75
32	41	14.2	6.0	73
16	44	14.2	7.8	71
16	49	15.0	7.6	69
32	49	14.3	7.8	67
16	59	14.5	8.7	65
32	59	12.4	8.1	64
26	63	13.7	8.8	62
16	67	13.9	9.9	60
32	69	11.6	6.8	57
16	73	13.8	11.8	58
32	78	12.5	10.7	55
16	82	12.5	10.8	55
26	82	12.8	12.6	52
32	86	9.8	10.7	48
32	89	10.9	11.9	49
16	92	11.3	11.8	50
32	97	8.6	10.3	46
32	100	8.0	12.2	40
26	101	10.2	11.9	47
26	116	9.6	15.0	40

$k_{obs.} = 1.28 \times 10^{-4}$ sec.$^{-1}$

Table 68. Deuterium Exchange in 0.211 M N-Methylmorpholine

0.211 M N-Methylmorpholine — 0.14 M Isobutyraldehyde-2-d

0.212 M N-Methylmorpholinium Ion — 0.22 M Sodium Perchlorate

Time (Minutes)	D_2	H_1	Per Cent D
4.8	18.8	1.5	96
15.3	19.6	2.3	93
25.0	22.3	3.6	90
40.8	21.0	3.5	90
55.5	20.6	5.1	84
69.5	19.0	4.7	84
83.8	20.4	5.8	81
96.0	19.2	6.8	77
117.0	18.1	6.7	76
128.8	18.4	7.9	73
143.5	17.4	7.9	71
160.0	17.1	9.3	67
182.0	14.8	9.5	63
206.5	14.9	9.8	62
231.8	14.5	11.2	58
265.0	13.0	11.2	55
281.5	12.9	11.5	54
293.5	12.3	11.7	52
306.5	11.7	23.9	50

$$k_{obs.} = 3.75 \times 10^{-5} \text{ sec.}^{-1}$$

Table 69. Deuterium Exchange in 0.211 M N-Methylmorpholine--0.132 M Methylammonium Ion

0.211 M N-Methylmorpholine

0.212 M N-Methylmorpholinium Ion

0.098 M Sodium Perchlorate

0.132 M Methylammonium Ion

0.14 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
20	19.0	3.6	88
21	19.5	3.4	89
24	19.2	4.0	87
34	18.4	4.9	83
35	18.3	6.0	79
40	16.7	5.1	80
41	18.3	5.6	80
47	17.5	6.4	76
48	17.7	6.8	75
55	16.8	7.5	72
59	17.2	7.8	72
66	16.0	8.4	68
72	16.7	9.9	65
77	15.0	9.4	64
85	13.2	8.4	61
100	13.9	10.9	58
110	13.0	11.2	55
118	15.5	14.2	54
123	14.5	14.9	52

$k_{obs.} = 9.55 \times 10^{-5}$ sec.$^{-1}$

Table 70. Deuterium Exchange in 0.211 M N-Methylmorpholine--0.176 M Methylammonium Ion

0.211 M N-Methylmorpholine

0.176 M Methylammonium Ion

0.212 M N-Methylmorpholinium Ion

0.14 M Isobutyraldehyde-2-d

0.044 M Sodium Perchlorate

Experiment Number	Time (Minutes)	D_2	H_1	Per Cent D
19	7.3	20.5	2.5	94
19	8.5	19.3	2.3	94
19	9.3	21.0	2.5	94
19	13.8	18.8	4.2	86
19	15.0	18.7	3.7	84
19	20.0	19.2	4.0	85
33	20.0	17.2	4.1	85
19	26.8	18.7	4.7	84
33	29.0	17.6	5.3	80
27	34.0	8.5	3.0	77
19	35.0	17.4	5.7	79
33	35.0	14.9	6.7	72
33	43.3	15.9	6.9	73
19	45.4	17.0	6.3	74
33	51.3	15.1	8.0	68
27	54.5	7.3	3.3	72
19	56.5	14.7	9.3	68
33	60.5	13.4	8.2	64
19	68.5	14.1	8.9	63
33	74.0	13.5	10.4	59
27	74.0	5.8	4.1	61
19	83.0	13.3	11.4	55
33	90.5	11.3	11.2	52
19	92.0	12.7	11.6	54
33	95.0	10.9	9.6	55
27	95.5	4.8	4.7	52
27	98.0	6.1	5.7	53
19	102.5	11.9	11.8	51
27	129.0	5.2	6.4	46

$k_{obs.} = 1.13 \times 10^{-4}$ sec.$^{-1}$

Table 71. Deuterium Exchange in 0.211 M N-Methylmorpholine--0.088 M Methylammonium Ion

0.211 M N-Methylmorpholine
0.212 M N-Methylmorpholinium Ion
0.132 M Sodium Perchlorate
0.088 M Methylammonium Ion
0.14 M Isobutyraldehyde-2-d

Exp. No.	Time (Mins.)	D_2	H_1	Per Cent D
20	4.5	17.9	2.5	89
20	7.3	19.0	1.8	95
20	14.0	20.6	2.2	94
20	23.0	19.7	3.0	91
20	32.0	18.8	4.2	86
28	37.0	8.9	2.8	80
20	43.5	18.4	5.3	81
28	57.5	7.7	3.3	73
20	54.3	17.3	6.3	76
20	63.3	16.4	6.7	74
28	75.0	6.7	4.5	62
20	76.3	16.0	7.1	72
20	80.0	16.3	7.5	71
20	87.3	14.4	7.5	68
20	102.5	14.7	8.8	65
20	115.0	14.2	10.2	60
28	116.0	5.3	4.6	56
20	123.0	13.1	10.2	58
20	135.3	12.5	11.1	55
28	143.0	5.2	4.9	53
20	151.0	12.3	11.5	53

$k_{obs.} = 7.31 \times 10^{-5}$ sec^{-1}

Table 72. Deuterium Exchange in 0.211 M N-Methylmorpholine--0.044 M Methylammonium Ion

0.211 M N-Methylmorpholine
0.212 M N-Methylmorpholinium Ion
0.176 M Sodium Perchlorate
0.044 M Methylammonium Ion
0.14 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
55	18.6	4.8	83
77	16.8	5.6	78
110	14.6	7.1	70
131	13.9	8.3	65
172	11.1	10.1	54
191	11.1	12.0	49

$k_{obs.} = 5.78 \times 10^{-5}$ sec^{-1}

Table 73. Deuterium Exchange in 0.187 M N-Methylmorpholine--0.030 M Methylammonium Ion

0.187 M N-Methylmorpholine
0.075 M N-Methylmorpholinium Ion
0.128 M Sodium Perchlorate
0.030 M Methylammonium Ion
0.22 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
20	21.0	3.9	88
31	22.5	4.9	86
34	21.9	4.5	87
67	21.5	6.4	80
70	22.4	6.2	82
106	18.8	9.0	71
140	18.7	11.4	65
143	14.7	7.5	69
172	17.6	13.0	60
198	18.3	14.7	57

$k_{obs.}$ 4.50×10^{-5} $sec.^{-1}$

Table 74. Deuterium Exchange in 0.187 M N-Methylmorpholine--0.070 M Methylammonium Ion

0.187 M N-Methylmorpholine
0.075 M N-Methylmorpholinium
0.22 M Isobutyraldehyde-2-d
0.070 M Methylammonium Ion
0.005 M Isobutyrate Ion
0.105 M Sodium Perchlorate

Time	D_2	H_1	Per Cent D
13.7	23.3	3.3	91.5
34.5	22.1	3.8	88.5
37.8	17.6	3.4	86.8
41.7	17.5	7.0	85.0
49.5	18.6	5.2	81.5
56.3	18.9	5.1	82.0
68.5	18.1	5.4	80.0
85.5	18.4	7.3	74.5
105.3	16.4	9.2	66.0
130.5	16.4	10.6	63.0
148.5	15.5	11.8	58.8
166.5	15.6	12.9	56.3
196.8	13.1	14.7	48.0
202.0	14.3	15.5	48.8
205.5	14.6	14.9	50.7
233.5	12.2	14.2	47.0

$k_{obs.} = 5.88 \times 10^{-5}$ $sec.^{-1}$

Table 75. Deuterium Exchange in 0.187 M N-Methylmorpholine--0.176 M Methylammonium Ion

0.187 M N-Methylmorpholine — 0.176 M Methylammonium Ion

0.075 M N-Methylmorpholinium Ion — 0.22 M Isobutyraldehyde-2-d

0 Sodium Perchlorate

Time (Minutes)	D_2	H_1	Per Cent D
7	22.3	3.8	89.0
14.3	21.4	3.8	88.0
17.8	21.5	4.2	87.5
33.0	20.2	6.1	80.3
51.0	19.1	7.8	74.0
67.3	17.2	8.4	66.5
84.5	16.0	10.3	62.0
116.0	13.0	12.5	52.0
149.0	10.7	13.1	45.0

$k_{obs.} = 9.9 \times 10^{-5}$ sec^{-1}

Table 76. Deuterium Exchange in 0.189 M N-Methylmorpholine--0.141 M Methylammonium Ion, Ionic Strength 0.342

0.189 M N-Methylmorpholine
0.073 M N-Methylmorpholinium Ion
0.152 M Sodium Perchlorate
0.141 M Methylammonium Ion
0.22 M Isobutyraldehyde-2-d

Time	D_2	H_1	Per Cent D
15	21.6	7.9	76
17.8	22.3	8.2	76
18.8	22.5	7.9	77
23.0	20.6	8.3	73
25.2	70.6	8.6	73
28.8	20.8	8.3	73
37.4	21.1	10.3	70
39.3	21.3	10.6	68
48.7	19.8	11.4	66
50.3	18.7	11.5	64
58.7	18.3	11.2	64
60.7	17.9	12.4	61
68.7	17.5	12.4	61
70.4	17.9	13.2	60
90.8	16.1	13.2	56
92.4	15.9	14.0	55
94.1	15.9	14.4	54
106.3	15.1	15.3	51
108.1	15.3	15.0	52
110.1	19.3	18.8	52
126.2	13.5	15.7	47
161.3	15.8	21.2	43
173.3	14.3	22.2	40
211.0	10.9	30.4	35
226.0	10.3	20.9	33

$k_{obs.} = 6.70 \times 10^{-5}$ sec^{-1}

Table 77. Deuterium Exchange in 0.189 M N-Methylmorpholine--0.141 M Methylammonium Ion, Ionic Strength 0.249

0.189 M N-Methylmorpholine

0.141 M Methylammonium Ion

0.073 M N-Methylmorpholinium

0.22 M Isobutyraldehyde-2-d

0.035 M Sodium Perchlorate

Time	D	H	Per Cent D
11.0	20.8	7.6	76
27.1	19.9	9.8	71
46.3	19.5	11.2	66
64.3	19.5	12.9	62
78.0	27.0	17.40	57
106.0	17.5	16.5	53
113.0	17.5	17.4	51
120.5	18.4	19.2	50
129.0	18.2	20.3	49
157.6	15.4	21.2	43
163.0	15.7	23.0	41

$k_{obs.} = 6.53 \times 10^{-5}$ sec.$^{-1}$

Table 78. Deuterium Exchange in 0.169 M N-Methylmorpholine--0.22 M Methylammonium Ion

0.169 M N-Methylmorpholine

0.145 M N-Methylmorpholinium Ion

0.036 M Sodium Perchlorate

0.22 M Methylammonium Ion

0.14 M Isobutyraldehyde-2-d

Experiment Number	Time (Minutes)	D_2	H_1	Per Cent D
4	4.3	21.6	2.3	95.0
9	12.5	23.2	2.8	93.0
9	24.0	22.0	5.0	85.0
4	28.0	20.3	5.5	82.3
9	34.5	21.2	5.7	82.3
4	36.5	17.8	6.3	77.0
4	43.5	18.5	6.7	76.5
9	50.0	22.7	10.5	71.0
4	57.0	17.2	8.3	70.0
4	63.0	18.9	10.2	67.5
9	66.5	20.5	13.2	63.0
4	70.0	16.9	9.5	66.3
9	79.0	15.8	11.3	60.0
9	97.5	16.6	15.5	53.0
4	102.0	14.9	13.6	54.0
9	116.0	15.6	17.3	48.5
4	152.0	13.6	17.1	45.0

$k_{obs.} = 1.05 \times 10^{-4}$ sec.$^{-1}$

Table 79. Deuterium Exchange in 0.127 M N-Methylmorpholine--0.22 M Methylammonium Ion

0.127 M N-Methylmorpholine
0.109 M N-Methylmorpholinium Ion
0.073 M Sodium Perchlorate
0.22 M Methylammonium Ion
0.14 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
20.0	20.9	3.5	91.0
28.5	18.3	4.6	83.8
34.0	19.7	5.1	82.8
38.5	20.1	5.4	81.8
58.0	18.6	8.1	72.5
85.0	15.0	8.8	65.3
96.0	17.7	11.5	62.8
132.5	13.3	12.0	54.0
136.0	13.0	13.4	50.3
154.5	12.0	12.9	49.0
168.5	10.6	13.8	44.0

$k_{obs.} = 8.13 \times 10^{-5}$ sec.$^{-1}$

Table 80. Deuterium Exchange in 0.084 M N-Methylmorpholine--0.22 M Methylammonium Ion

0.084 M N-Methylmorpholine
0.073 M N-Methylmorpholinium Ion
0.109 M Sodium Perchlorate
0.22 M Methylammonium Ion
0.14 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
22.5	19.9	2.3	94
39.5	20.1	4.1	86.8
63.5	23.6	7.0	80.3
95.5	17.2	7.3	72.5
114.0	15.8	7.2	71.5
134.0	16.3	8.5	68.0
165.5	13.5	10.8	57.3
183.5	14.5	11.3	57.8
203.5	13.5	12.7	54.0
261.5	13.7	15.6	47.5

$k_{obs.} = 5.15 \times 10^{-5}$ sec.$^{-1}$

Table 81. Deuterium Exchange in 0.211 M N-Methylmorpholine--0.22 M Methylammonium Ion

0.211 M N-Methylmorpholine
0.182 M N-Methylmorpholinium Ion
0 Sodium Perchlorate
0.22 M Methylammonium Ion
0.14 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
17.0	23.1	5.1	85.5
26.0	21.1	6.4	80.0
32.3	19.9	6.9	77.5
42.2	17.4	9.9	66.0
51.0	16.5	10.6	63.0
62.0	16.7	11.0	62.5
65.3	16.4	12.1	59.3
76.0	15.6	14.8	52.5
92.3	15.3	17.7	47.0
106.0	12.6	17.6	40.0

$k_{obs.} = 1.37 \times 10^{-4}$ sec.$^{-1}$

Table 82. Deuterium Exchange in 0.154 M N-Methylmorpholine--0.22 M Methylammonium Ion

0.154 M N-Methylmorpholine
0.424 M N-Methylmorpholinium Ion
0 Sodium Perchlorate
0.22 M Methylammonium Ion
0.14 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
17.8	22.0	4.6	86.0
47.0	15.2	6.2	74.0
59.0	16.0	8.8	67.0
61.5	18.1	10.1	66.5
63.8	17.8	12.0	64.0
78.5	16.7	13.5	57.3
92.3	15.0	13.5	54.3
107.0	13.6	15.2	48.0
122.8	12.3	16.6	43.0

$k_{obs.} = 1.12 \times 10^{-4}$ sec.$^{-1}$

Table 83. Deuterium Exchange in 0.106 M N-Methylmorpholine--0.22 M Methylammonium Ion

0.106 M N-Methylmorpholine
0.091 M N-Methylmorpholinium Ion
0.091 M Sodium Perchlorate
0.22 M Methylammonium Ion
0.14 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
65	21.9	8.3	75.3
79	19.3	8.8	72.5
81	20.7	9.5	73.3
100	19.8	10.8	67.0
112	18.4	10.9	65.0
128	19.4	12.8	62.0
145	16.9	14.8	54.5
150	20.3	17.4	55.3
173	19.0	17.5	50.5
191	16.5	20.4	45.5

$k_{obs.} = 6.75 \times 10^{-5}$ sec.$^{-1}$

Table 84. Deuterium Exchange in 0.167 M N-Methylmorpholine--0.22 M Methylammonium Ion

0.167 M N-Methylmorpholine
0.168 M N-Methylmorpholinium Ion
0.042 M Sodium Perchlorate
0.22 M Methylammonium Ion
0.14 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
23	15.7	3.4	86
41	11.2	3.4	80
55	14.7	6.3	73
76	11.1	6.6	65
79	12.9	8.2	63
87	13.0	9.4	60
103	9.9	8.7	55
104	11.6	9.7	56
116	11.5	11.3	52
126	11.2	11.7	50
142	10.1	12.6	45

$k_{obs.} = 9.33 \times 10^{-5}$ sec.$^{-1}$

Table 85. Deuterium Exchange in 0.125 M N-Methylmorpholine--0.22 M Methylammonium Ion

0.125 M N-Methylmorpholine

0.126 M N-Methylmorpholinium Ion

0.084 M Sodium Perchlorate

0.22 M Methylammonium Ion

0.14 M Isobutyraldehyde-2-d

Time (Minutes)	D_2	H_1	Per Cent D
27	16.5	3.2	88
60	14.2	5.3	76
63	14.0	5.3	76
98	12.8	7.6	65
133	11.0	9.7	55
149	8.7	8.9	51
174	8.6	11.0	45

$k_{obs.} = 7.50 \times 10^{-5}$ sec.$^{-1}$

NUCLEAR MAGNETIC RESONANCE SPECTRA

Tetramethylsilane was used as an internal reference in the neat spectra and those using carbon tetrachloride. Sodium 3-(trimethylsilyl)-1-propanesulfonate was used as an internal reference in all aqueous spectra.

The following abbreviations will be used with the nuclear magnetic resonance spectra:

S.T. = Sweep Time	R.F.F. = R. F. Field
S.W. = Sweep Width	S.O. = Sweep Offset
F.B. = Filter Bandwidth	S.A. = Spectrum Amp.

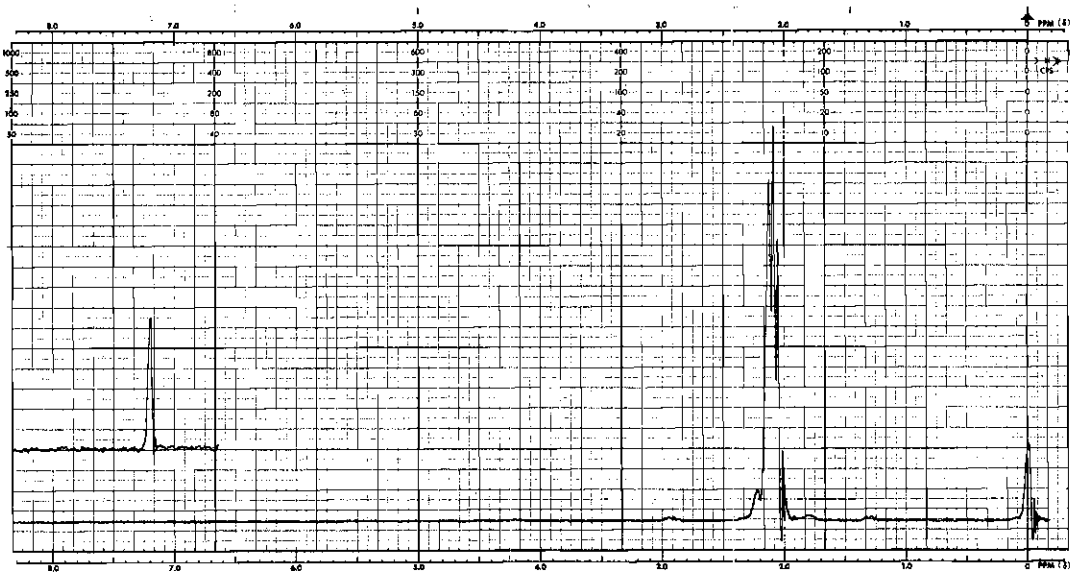

Figure 7. Nuclear Magnetic Resonance Spectrum of Isobutyraldehyde-2-d Neat. F.B.: 4 c.p.s.; R.F.F.: 0.02 mG.; S.T.: 250 sec.; S.W.: 250 c.p.s.; S.A.: 0.50; Insert S.O.: 350 c.p.s.

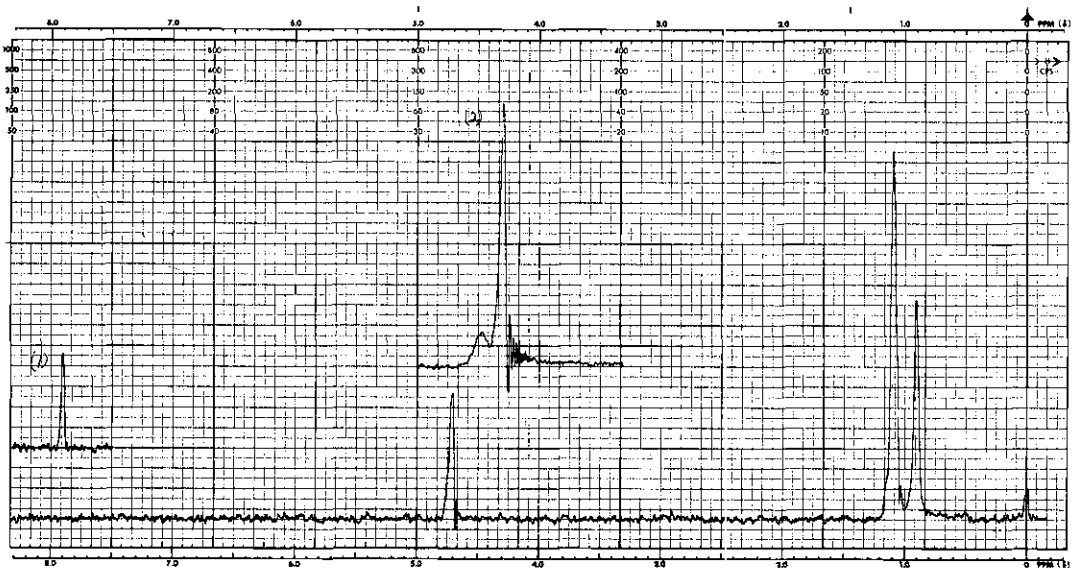

Figure 8. Nuclear Magnetic Resonance Spectrum of Isobutyraldehyde-2-d in Deuterium Oxide. F.B.: 4 c.p.s.; R.F.F.: 0.05 mG.; S.T.: 250 sec.; S.W.: 500 c.p.s.; S.A.: 12.5; Insert 1 S.O.: 100 c.p.s.; Insert 2: S.W.: 100 c.p.s.; S.O.: 250 c.p.s.

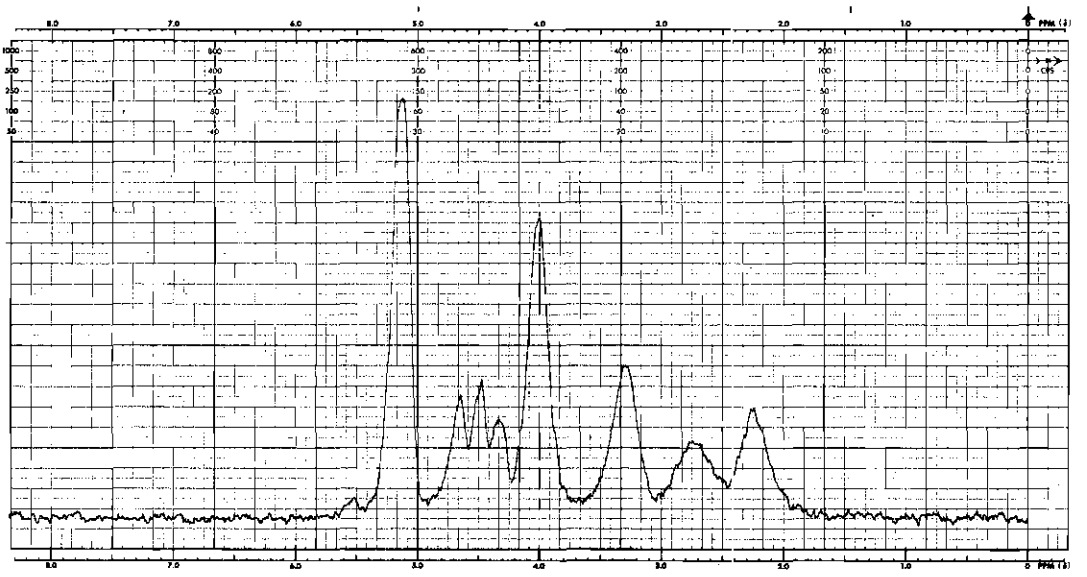

Figure 9. Nuclear Magnetic Resonance Spectrum of a Mixture of Isobutyraldehyde and Isobutyraldehyde-2-d in Deuterium Oxide. F.B.: 0.4 c.p.s.; R.F.F.: 0.02 mG.; S.T.: 250 sec.; S.W.: 50 c.p.s.; S.A.: 10; S.O.: 40 c.p.s.

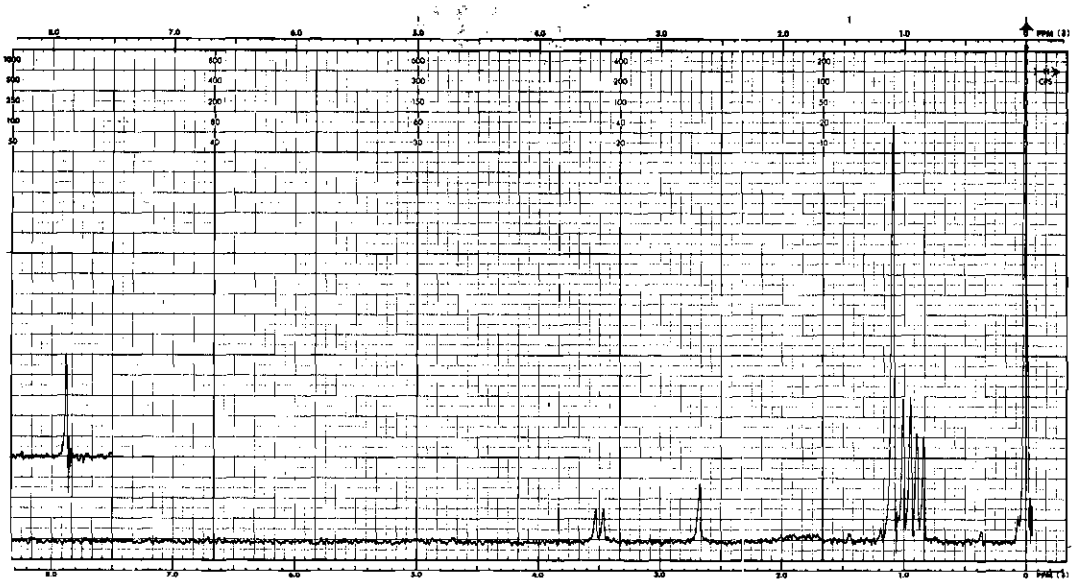

Figure 10. Nuclear Magnetic Resonance Spectrum of Isobutyraldol in CCl_4. F.B.: 2 c.p.s.; R.F.F.: 0.02 mG.; S.T.: 250 sec.; S.W.: 500 c.p.s.; S.A.: 3.2; Insert S.O.: 100 c.p.s.

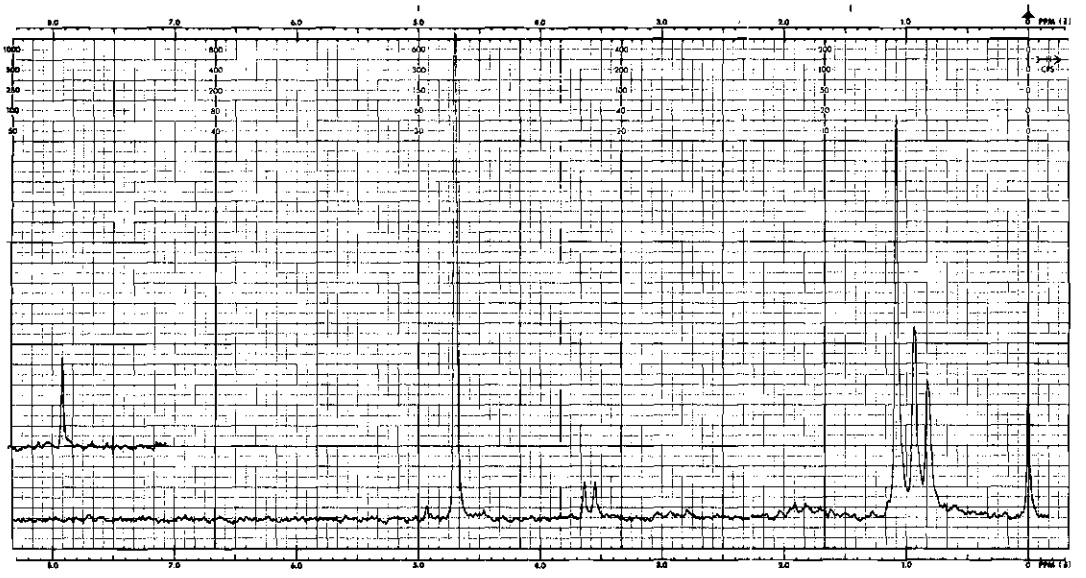

Figure 11. Nuclear Magnetic Resonance Spectrum of Isobutyraldol in Deuterium Oxide. F.B.: 0.4 c.p.s.; R.F.F.: 0.05 mG.; S.T.: 250 sec.; S.W.: 500 c.p.s.; S.A.: 16; Insert S.O.: 100 c.p.s.

LITERATURE CITED

1. C. G. Swain and J. F. Brown, Jr., *Journal of the American Chemical Society, 74,* 2534 (1952).

2. F. H. Westheimer and H. Cohen, *ibid., 60,* 90 (1938).

3. F. H. Westheimer, *Annals of the New York Academy of Sciences, 39,* (Art. 5), 401 (1940).

4. J. Hine, *Physical Organic Chemistry, 2nd ed.,* McGraw-Hill Book Co., Inc., New York, N. Y., 1962, sec. 5-2B.

5. R. P. Bell, *The Proton in Chemistry,* Cornell University Press, Ithaca, N. Y., 1959, p. 143.

6. J. N. Bronsted, *Chemical Reviews, 5,* 231 (1928).

7. R. G. Pearson and F. V. Williams, *Journal of the American Chemical Society, 75,* 3073 (1953).

8. *Ibid., 76,* 258 (1954).

9. E. S. Lewis and J. D. Allen, *ibid., 86,* 2022 (1964).

10. J. A. Feather and V. Gold, *Proceedings of the Chemical Society, 1962,* 306.

11. R. P. Bell and G. T. Wilson, *Transactions of the Faraday Society, 46,* 407 (1950).

12. R. P. Bell, M. H. Rand and K. M. A. Wynne-Jones, *ibid., 52,* 1093 (1956).

13. R. P. Bell and M. B. Jenson, *Proceedings of the Royal Society* (London), *A261,* 38 (1961).

14. F. H. Westheimer and F. Covitz, *Journal of the American Chemical Society, 85,* 1773 (1963).

15. V. Gold, *Progress in Stereochemistry, Vol. 3,* Butterworths, London, 1962, p. 169.

16. K. J. Pedersen, *Journal of Physical Chemistry, 38,* 559 (1934).

17. *Ibid., Journal of the American Chemical Society, 60,* 595 (1938).

18. E. O. Wiig, *Journal of Physical Chemistry, 32,* 961 (1928).

19. W. Franke and G. Brathuhn, *Annalen der Chemie, Justus Liebigs, 487,* 1 (1931).

20. F. H. Westheimer and W. A. Jones, *Journal of the American Chemical Society, 63,* 3283 (1941).

21. S. Matsumato, *Technical Bulletin of the Kagawa Agricultural College (Japan), 5,* 103 (1953); *Chemical Abstracts, 49,* 7493i, (1955).

22. F. H. Westheimer and I. Fridovich, *Journal of the American Chemical Society, 84,* 3208 (1962).

23. E. H. Usherwood, *Journal of the Chemical Society, 123,* 1717 (1923).

24. E. A. Shilov and A. A. Yasnikov, *Ukrainskii Khimicheskii Zhurnal, 27,* 639 (1961).

25. H. S. Gutowsky, M. Karplus and D. M. Grant, *Journal of Chemical Physics, 31,* 1278 (1959).

26. R. H. Saunders, M. J. Murray, and F. F. Cleveland, *Journal of the American Chemical Society, 65,* 1714 (1943).

27. H. J. Hagemeyer, G. V. Hudson, S. H. Johnson, M. B. Edwards and H. N. Wright, American Chemical Society, Division of Petroleum Chemistry, Preprints--Symposia *1,* No. 2, 63 (1956).

28. M. Häring, *Helvetica Chimica Acta, 42,* 1845 (1959).

29. C. M. Judson and M. Kilpatrick, *Journal of the American Chemical Society, 71,* 3110 (1949).

30. R. R. Dreisbach and S. A. Shrader, *Industrial and Engineering Chemistry, 41,* 2879 (1949).

31. R. D. Cadle, B. J. Robson and R. W. Moshier, *Journal of the American Chemical Society, 71,* 2928 (1949).

32. D. I. Coomber and J. R. Partington, *Journal of the Chemical Society, 1938,* 1444.

33. E. A. Coulson, J. D. Cox, E. F. G. Herington and J. F. Martin, *ibid., 1959,* 1934.

34. D. D. Reynolds and W. O. Kenyon, *Journal of the American Chemical Society, 72,* 1597 (1950).

35. S. Searles, M. Tamres, F. Block and L. A. Quarterman, *ibid., 78,* 4917 (1956).

36. D. P. Biddiscombe, E. A. Coulson, R. Handley and E. F. G. Herington, *Journal of the Chemical Society, 1954,* 1957.

37. L. Spialter and R. W. Moshier, *Journal of the American Chemical Society, 79,* 5955 (1957).

38. R. Dworzak and J. Pierri, *Monatshefte für Chemie und verwandte Tiele anderer Wissenschaften, 52,* 145 (1929).

39. J. Hine, N. W. Burske, M. Hine and P. B. Langford, *Journal of the American Chemical Society, 79,* 1406 (1957).

40. J. F. Masi and S. B. Knight, *ibid., 67,* 1558 (1945).

41. D. H. Everett, D. A. Landsman and B. R. Pinsent, *Proceedings of the Royal Society (London), A215,* 403 (1952).

42. R. P. Bell and P. T. McTigue, *Journal of the Chemical Society, 1960,* 2983.

43. R. P. Bell and D. P. Onwood, *ibid., 1962,* 1557.

44. R. Stewart and R. Van der Linden, *Canadian Journal of Chemistry, 38,* 399 (1960).

45. P. Ballinger and F. A. Long, *Journal of the American Chemical Society, 82,* 795 (1960).

46. R. P. Bell and D. P. Onwood, *Transactions of the Faraday Society, 58,* 1557 (1962).

47. J. Murto, *Annales Academiae Scientiarum Fennicae, A.II,* 117 (1962).

48. S. W. Benson, *Journal of the American Chemical Society, 80,* 5151 (1958).

49. M. S. Newman, ed., *Steric Effects in Organic Chemistry,* John Wiley and Sons, Inc., New York, N. Y., 1956, p. 592.

50. R. W. Taft, Jr., *Journal of the American Chemical Society, 75,* 4231 (1953).

51. J. Hine and M. Hine, *ibid., 74,* 5266 (1952).

52. J. D. Roberts, *Nuclear Magnetic Resonance,* McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 30.

53. A. A. Frost and R. G. Pearson, *Kinetics and Mechanisms, 2nd ed.,* John Wiley and Sons, Inc., New York, N. Y., 1961, p. 186.

54. W. Herold, *Zeitschrift fuer Physikalische Chemie, 18B,* 265 (1932).

55. J. Hine, *Physical Organic Chemistry, 2nd ed.*, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, sec. 11-3b.

56. H. K. Hall, *Journal of Physical Chemistry, 60,* 63 (1956).

57. M. L. Bender and B. W. Tarnquest, *Journal of the American Chemical Society, 79,* 1656 (1957).

58. R. P. Bell, *The Proton in Chemistry,* Cornell University Press, Ithaca, N. Y., 1959, p. 175.

59. D. H. Everett and W. F. K. Wynne-Jones, *Proceedings of the Royal Society (London), A177,* 499 (1941).

60. E. Grunwald and B. J. Berkowitz, *Journal of the American Chemical Society, 73,* 4939 (1951).

61. R. J. L. Andon, J. D. Cox and E. F. G. Herington, *Transactions of the Faraday Society, 50,* 918 (1954).

62. A. I. Biggs and R. A. Robinson, *Journal of the Chemical Society, 1961,* 388.

63. N. F. Hall, *Journal of the American Chemical Society, 52,* 5115 (1930).

64. J. Hansson, *Svensk Kemisk Tidskrift, 67,* 256 (1955).

65. A. Gero and J. J. Markham, *Journal of Organic Chemistry, 16,* 1835 (1951).

66. R. G. Bates and G. Schwarzenbach, *Helvetica Chimica Acta, 37,* 1437 (1954).

67. P. Nylén, *Zeitschrift für anorganische und allgemeine Chemie, 246,* 227 (1941).

68. E. A. Braude and F. C. Nachod, *Determination of Organic Structures by Physical Methods, Vol. 1,* Academic Press Inc., New York, N. Y., 1955, chap. 14.

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